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METABOLISM IN PELLAGRA: A STUDY OF THE URINE

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It is now well established that diet, according to its qualitative and quantitative nature, plays a most important part in the prevention, causation and cure of pellagra. Certain types of diet have been proved experimentally to be provocative of pellagra,[1] while in the Pellagra Hospital the treatment of the disease has been absolutely dietary.

Considering the part that diet, good or bad as the case may be, plays in pellagra, it would seem that whatever new facts are added to our knowledge of metabolism in pellagra would decidedly be worth while, particularly in view of the fact that the investigations of metabolism in this disease have not been extensive.

Camurri appears to be the first to have made a comprehensive study of metabolism [2] in pellagra. His work dealt particularly with the mineral metabolism. He states that the diet of the Italian pellagrins is lacking in sodium and calcium. Camurri's work included, also, a study of the composition of the diet, of the urine, and feces of pellagrins subsisting on mixed diets and on diets composed largely of corn. Balances were obtained for nitrogen, fat and salts in comparison with those of normal individuals on similar diets. In pellagra he found an increase in the excretion of chlorin estimated as sodium chlorid. Nicolaidi and Grillo [3] found a decided negative mineral balance in active pellagra. Myers and Fine,[4] in their extensive investigations of metabolism in pellagra, found that the ability of individuals suffering from pellagra to utilize the various foodstuffs was but slightly, if at all, below the normal.

1. Goldberger and Wheeler: Experimental Pellagra in the Human Subject Brought About by a Restricted Diet, Pub. Health Rep. **30**: No. 46 (Nov. 13) 1915; Bull. 120, Hyg. Lab. Washington, 1920.

2. Camurri: Atti del quarto Congresso Pellagrologico, Italiana, Udine, 1910, p. 67.

3. Nicolaidi and Grillo: Tr. Nat. Assn. for Study of Pellagra, Triennial Meeting, Columbia, S. C., 1912, p. 127.

4. Myers and Fine: Am. J. M. Sc. **145**:705, 1913.

Nitrogen balances with different diets were likewise studied by Hunter, Givens and Lewis [5] at the Pellagra Hospital. They conclude that "A diet providing 2,500 calories and containing 15 gm. nitrogen (of which 11 gm. are in the form of animal protein) is not only likely to promote the recovery of the pellagrin from an acute attack but is adequate to meet all the requirements, for maintenance and repair of his convalescence."

The frequent occurrence of gastric anacidity was noted by Johnson,[6] Ceconni,[7] Niles,[8] Myers and Fine, Hunter, Givens, and Lewis, and the presence of an excessive quantity of indican in the urine has been reported repeatedly, especially in the urine of American pellagrins. Myers and Fine concluded that the indicanuria is excessive in the cases with gastric inefficiency. Hunter, Givens, and Lewis, however, show that gastric inefficiency is only one of the factors involved in indican formation and that a very important factor is to be found in the patient's diet—the tendency to excessive indican formation being greater on a meat diet. They show further that the existence of pellagra is compatible with any degree whatever of indican production, even none at all and that indicanuria, undeniably a common feature of the disease, is by no means an essential one.

That indicanuria is not an essential factor in pellagra is shown also by the findings of Goldberger and Wheeler. Thus, in 1915 Goldberger and Wheeler [1] showed that pellagra could be produced experimentally in previously healthy human subjects by feeding a restricted one-sided mainly cereal diet of the type found to be associated with a high incidence of pellagra. The urine of their subject contained little if any indican while they were on the pellagra producing diet.

In the work herein described, a survey of the urine of pellagra patients was made as soon as possible after the patient's admission to the hospital and in some cases at the time of applying for admission to the hospital and before actual admission. Attention was paid to the variation in normal constituents, the presence of physiologic bases, and the presence of abnormal constituents.

Once started, the variation in normal and abnormal constituents was followed from the acute highly erythematous stage to the stage with a high degree of improvement or discharge from the hospital as recovered. In some of the lines of work started the results are fragmentary because of loss of personnel on account of the war. In this paper, however, are reported results of a study of the specific gravity, volume, total nitrogen, ammonia, creatinin, urea and uric acid.

5. Hunter, Givens, and Lewis: Bull. 102, II, Hygienic Lab. U. S. P. H. S., 1916.
6. Johnson: South. M. J. **4**:578, 1911.
7. Ceconni: Gazz. d. osp. **32**:77, 1911.
8. Niles: Pellagra, 1912, p. 77.

The methods employed were: for total nitrogen, Kjeldahl; for ammonia, Folin's [9] method as modified by Steel [10]; creatinin by Folin's method [11]; uric acid by the Folin-Shaffer [12] method; urea by Folin and Denis' method [13] using jack bean as a source of urease, and a reaction temperature of from 50 to 55 C. The urine of four normal persons was tested in a similar way at the same time.

Except for short periods, the normal individuals were under uncontrolled conditions with great variation in diet and with a mode of living quite different from that of the patients. Accordingly, considering that metabolism is more or less an individual question, it was concluded that the best control for the patients in active pellagra is the same patient at or about the time of discharge, when they showed no sign or symptom, which, in the judgment of the medical staff, would indicate a pellagrous condition. Much emphasis is put, therefore, on the comparison of data obtained just after the patient was admitted to the hospital and the data obtained just before the patient was to be discharged.

The patients in the hospital in 1917 were good cases of pellagra. The treatment in the hospital of uncomplicated cases, the only kind considered in this study, was entirely dietary. Two types of diet were employed during 1917, diet G and diet B as follows:

TABLE 1.—TYPES OF DIETS GIVEN PELLAGRINS

Diet G	Gm.	N	Calories	Diet B	Gm.	N	Calories
Loaf bread	300	4.02	864	Loaf bread	300	4.02	864
Butter	45	0.034	356	Butter	45	0.034	356
Corn meal	50	0.670	190	Corn meal	50	0.670	190
Hominy grits	50	0.638	181	Eggs	100	2.200	153
Round steak	100	3.540	120	Round steak	100	3.540	120
Ham	25	1.110	62	Orange juice	50	0.073	19
Orange juice	50	0.073	19	Potato	150	0.525	126
Potato	100	0.350	84	Dried apple	50	0.105	149
Dried apple	50	0.105	149	Milk, 1,000 c.c.	...	5.400	735
Cabbage	50	0.161	16	Coffee, c.c.	175	0.087	
Squash	50	0.112	24	Sugar	20	.....	82
Milk, c. c.	400	2.160	294	Pork fat	19	.....	177
Coffee, c.c.	175	0.087					
Sugar	20	.....	82				
Pork fat	22	.....	205				
Total	.....	13.010	2,646	Total	.....	16.604	2,971

The total nitrogen and caloric values are based on analyses of the foodstuffs used at the Pellagra Hospital as given by Hunter, Givens and Lewis, and by Sullivan and Jones.[14] The calories for apple and squash are based on Atwater and Bryant's figures.

In general, at entrance to the hospital, the patients were placed on diet G, which contained 13.01 gm. nitrogen representing 81 gm. protein, of which approximately 6.84 gm. nitrogen or 42.8 gm. protein were of

9. Folin: Am. J. Physiol. **45**:13, 1905.
10. Steel: J. Biol. Chem. **8**:365. 1910.
11. Folin: Ztschr. f. physiol. Chem. **41**:223, 1904.
12. Folin-Shaffer: Ztschr. f. physiol. Chem. **32**:552, 1901.
13. Folin-Denis: J. Biol. Chem. **26**:501, 1916.
14. Bull. 120, II, Hygienic Laboratory, Washington, 1920.

animal origin. Then as the patients' appetite and demand for food became greater, they were placed on diet B containing 16.604 gm. nitrogen or approximately 103.78 gm. protein, of which 67 per cent. were of animal origin. Diet B, containing a higher protein content and a higher caloric value, was the more curative. However, a number of patients kept on diet G recovered from acute pellagra rapidly. In fact, the improvement in well being and the subsidence of pellagra symptoms showed that diet G, providing 2,600 calories and containing 13 gm. nitrogen, of which 6.84 gm. are from animal protein, suffices to eradicate the signs and symptoms which, in the judgment of the medical staff, are characteristic of pellagra.

June 22, 1917, a preliminary study was started on all the patients in the hospital to determine wherein the patients differed from normal people. Lombroso, as quoted by Marie,[15] found that in all his cases the phosphate of the urine was diminished in spite of good nutrition. Camurri likewise found the phosphate of the urine of pellagrins less than that of normal people. Camurri also found that the proportion of urea to total nitrogen was diminished, and that the ratio of ammonia nitrogen to total nitrogen was increased particularly in cases where the diet was predominantly a maize diet. Myers and Fine found that the elimination of total nitrogen, urea, ammonia, uric acid and creatinin is slightly below the normal, though the constituents dependent on exogenous origin, namely, the uric acid and creatinin, are such as might be observed in other persons of similar physical condition. Their data for the percentage of ammonia and undetermined nitrogen are slightly above the so-called normal figures, and the other constituents are slightly below, differences which they interpret as due to the diet and the physical condition of the patients.

In our preliminary work, it was found that the excretion of phosphates by the pellagra patients, even on a very good diet with a high milk content, was less than that of normal people. As the patient improved in general condition, and pellagra symptoms disappeared, the excretion of phosphates in the urine increased. This increase in the excretion of phosphates is tied up undoubtedly with a greater assimilation of food, and, perhaps, though this point was not tested, with an improved functioning of the kidneys. In the preliminary period the excretion of total amino-acid nitrogen as determined by the Van Slyke gasometric method[16] varied from 0.126 to 0.335 gm. amino-nitrogen with an average of 0.211 gm., or 3 per cent., of the total nitrogen for the active cases; from 0.148 to 0.516 gm., with an average of 0.271 gm., for the convalescing and the cases about to be discharged, and

15. Marie: Pellagra, Translated by Lavinder and Babcock, Columbia, S. C., 1910.

16. J. Biol. Chem. **16**:125, 1913.

from 0.136 to 0.310 gm. with an average of 0.214 gm. for the four normals.

According to Murlin [17] the absolute amount of mon-amino-acid nitrogen in the urine of normal persons on a mixed diet is from 0.15 to 0.30 gm. per day. This fact, coupled with the results from normal urines here, shows that the total amino-acid nitrogen of the twenty-four hour urine is normal in amount both in active and convalescing cases of pellagra. The latter ran somewhat higher, but the difference is in accord with the high milk diet on which the convalescent patients had been for a longer time for, as shown by Long and Gephart,[18] on a milk diet, the fraction of undetermined nitrogen, which includes the amino-acid nitrogen, is higher than on ordinary mixed diet.

For the patients, in general, but especially for the acute cases recently admitted, the total nitrogen of the preliminary period was low, the excretion of ammonia tended to be increased, and the ratio of ammonia nitrogen to total nitrogen was high. As the patients improved, the ammonia excretion and the ammonia ratio returned to normal and was within normal limits some times before the patients were discharged. The data for phosphates, amino-acids, total nitrogen, and ammonia for the preliminary period are given in Tables 2, 3 and 4. The preliminary study suggested that the study of the nitrogen partition of the urine would be profitable.

TABLE 2.—PHOSPHORIC ACID (P_2O_5) CONTENT OF URINE IN GRAMS; (A) FIRST TEST; (B) LAST TEST

Case	Date of Admission	Date of Discharge	Status of Pellagra at Time of Testing	Date of Test				
				6/28	7/2	7/5	7/9	7/13
				P_2O_5, Gm.	P_2O_5, Gm.	P_2O_5, Gm.	P_2O_5, Gm.	P_2O_5, Gm.
337	6/13	8/21	Active pellagra	.....	(a)0.964	1.648	1.328	(b)1.958
338	6/13	8/17	Active pellagra	(a)0.821	0.802	0.891	1.470	(b)1.920
341	6/24	8/25	Active pellagra	(a)1.734	1.743	.....	1.393	(b)1.940
347	6/27	8/ 9	Active pellagra	.....	.....	(a)0.900	1.018	(b)1.402
352	7/ 2	7/ 6	Active pellagra	.....	.....	0.764*		
318	5/12	7/14	Convalescent	.....	.....	(a)1.285	1.008	(b)1.712
323	5/21	7/16	Convalescent	.....	(a)1.376	1.167	1.749	(b)2.567
325	5/26	8/20	Convalescent	.....	(a)1.168	1.330	1.331	(b)1.626
328	5/29	8/20	Convalescent	.....	.....	.....	.....	2.005
Controls								
1	....	....	Nonpellagrous	(a)1.887	1.630	.....	.....	(b)2.233
2	....	....	Nonpellagrous	(a)2.939	2.140	2.958	1.877	(b)2.159
3	....	....	Nonpellagrous	.....	(a)1.565	1.870	1.681	(b)2.348
4	....	....	Nonpellagrous	.....	.....	.....	(a)1.365	(b)1.735

Average first tests active pellagra patients exclusive of case 352	1.105
Average last tests active pellagra patients exclusive of case 352	1.805
Average first tests convalescent patients exclusive of case 328	1.275
Average last tests convalescent patients exclusive of case 328	1.968
Average first tests controls	1.939
Average last tests controls	2.119

* Left hospital unimproved.

17. Murlin: Bull. 116, III, Hygienic Laboratory United States Public Health Service, 1920.

18. Long and Gephart: J. Am. Chem. Soc. **34**:1229, 1912.

TABLE 3.—Amino-Acid Nitrogen Content of the Urine

Case	Date of Admission	Status of Pellagra at Time of Testing	Date of Tests					
			6/23	6/28	7/2	7/5	7/9	7/13
			Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.
323	6/ 6	Active pellagra	0.195					
337	6/13	Active pellagra	.....	0.252	.....	0.225	0.273	0.335
338	6/13	Active pellagra	0.214	0.225	.....	0.219	0.179	0.161
339	6/15	Active pellagra	0.136					
341	6/24	Active pellagra	.....	0.169	.....	0.162	0.268	0.107
347	6/27	Active pellagra	.....	.....	.....	0.185	0.237	0.227
352	7/ 2	Active pellagra	.....	.....	.....	0.225		
318	5/12	Convalescent	.....	0.225	.....	0.286	0.180	0.325
319	5/12	Convalescent	0.305	0.283				
323	5/21	Convalescent	.....	0.234	0.148	0.345	0.492	0.195
324	5/24	Convalescent	.....	0.516				
325	5/26	Convalescent	.....	0.263	0.222	0.287	0.228	0.201
328	5/29	Convalescent	.....	.....	.....	.....	.....	0.181
332	6/ 4	Convalescent	0.229					
Controls								
1	....	Nonpellagrous	.....	0.136	0.248	.....	.....	0.218
2	....	Nonpellagrous	.....	.....	0.202	0.237	0.263	0.286
3	....	Nonpellagrous	.....	0.151	.....	0.310	0.179	0.163
4	....	Nonpellagrous	.....	.....	.....	.....	0.170	

Average of tests of pellagra patients	0.211
Average of tests of convalescent patients	0.271
Average of tests of controls	0.214

TABLE 4.—Preliminary Period. Total Nitrogen, Ammonia Nitrogen, and Ammonia N Ratio to Total Nitrogen

Case	Date Admitted	Total Nitrogen, Gm.				Ammonia Nitrogen, Gm.				Ammonia N to Total Nitrogen, per Cent.			
		6/23	6/28	7/5	7/9	6/22	6/27	7/5	7/9	6/22	6/27	7/5	7/9
Active													
331	6/ 4	9.022	.....	.....	.....	0.684	.....	.....	.....	7.58			
333	6/ 6	7.448	.....	.....	.....	1.502	.....	.....	.....	20.17			
337	6/13	8.439	7.310	10.575	9.780	1.497	1.399	1.619	1.126	17.74	19 14	15.31	11.51
338	6/13	4.782	6.431	6.481	8.395	0.987	1.243	1.099	1.091	20.64	19.33	16.96	13.00
339	6/15	8.439	.....	.....	.....	0.507	.....	.....	.....	6.01			
341	6/24	.....	5.936	3.955	5.479	.....	0.724	0.705	0.593	.....	12.20	17.83	10.82
347	6/27	.....	.....	5.590	6.890	.....	.....	0.409	0.328	.....	.....	7.14	4.76
352	7/ 2	.....	.....	7.420	.....	.....	.....	0.595	.....	.....	.....	8.02	
Average	.....	7.626	6.559	6.804	7.636	1.035	1.122	0.885	0.785	14.43	16.80	13.05	10.02
Convalescing													
312	5/ 1	12.527	.....	.....	.....	0.736	.....	.....	.....	5.88			
318	5/12	8.859	8.727	10.805	15.730	0.477	0.578	0.927	0.824	5.38	6.62	8.58	5.24
319	5/12	13.940	15.752	.....	.....	0.890	0.998	.....	.....	6.38	6.34		
323	5/21	13.026	11.146	9.499	12.044	0.927	0.854	0.995	0.913	7.12	7.66	10.47	7.58
324	5/24	8.180	8.932	.....	.....	1.390	0.911	.....	.....	17.00	10.20		
325	5/26	10.881	6.185	10.410	10.158	1.374	1.170	0.882	0.610	12.63	18.90	8.47	6.01
327	5/27	7.448	.....	.....	.....	0.692	.....	.....	.....	9.29			
330	6/ 2	9.699	.....	.....	.....	1.137	.....	.....	.....	11.72			
332	6/ 4	9.839	.....	.....	.....	0.839	.....	.....	.....	8.53			
Average	.....	10.489	10.148	10.238	12.644	0.940	0.902	0.935	0.782	9.33	9.94	9.17	6.28
Controls Nonpellagrous													
1	.....	11.262	10.065	.....	.....	0.600	0.572	.....	.....	5.33	5.68		
3	.....	14.902	15.120	15.890	12.946	0.958	0.783	0.889	0.882	6.43	5.18	5.66	6.35
3	.....	13.882	9.052	15.060	10.566	0.575	0.348	0.741	0.490	4.14	3.84	4.92	4.64
4	.....	9.162	8.856	.....	7.072	0.431	0.445	.....	0.379	4.70	5.02	.....	5.36
Average	...	12.302	10 773	15.475	10.195	0.641	0.537	0.820	0.564	5.15	4.93	5.29	5.45

TABLE 5.—Composition of the Urine of Pellagrins: (A) at or Near the Time of Admission; (B) at or Near the Time of Discharge from the

TABLE 5.—Composition of the Urine of Pellagrins; (a) at or Near the Time of Admission; (b) at or Near the Time of Discharge from the Hospital; Arranged According to the Severity of the Symptoms

Case Number	Age, Years	Sex	Date of Admission	Date of Discharge	Duration of Testing	Status of Pellagra at Time of Testing	Weight at Beginning of Study, Kg.	Weight at End of Study, Kg.	Qualitative and Microscopic Examination		Volume of Urine, C.c.	Specific Gravity	Total Nitrogen	Ammonia Nitrogen, Gm.	Uric Acid Nitrogen	Creatinin Nitrogen	Urea Nitrogen, Gm.	Undetermined Nitrogen, Gm.	In Percentage of Total Nitrogen: Urea N	Ammonia N	Uric Acid N	Creatinin N	Undetermined N	Indican	Creatinin Coefficient	Diarrhea at Time of Testing	Diet
341	18	F	6/24/17	8/25/17	7/12–8/16	Severe	44.650	47.35	Negative	a	4,120	1.006	6.576	0.758	0.002	0.186	4.681	0.949	71.18	11.53	0.03	2.83	14.43	++	4.17	No	B
										b	3,815	1.009	9.200	0.473	0.010	0.196	6.761	1.760	73.49	5.14	0.11	2.13	19.13	+	4.14		B
353	36	F	7/ 9/17	8/19/17	7/26–8/16	Severe	43.350	44.35	Albumin	a	560	1.017	4.026	0.357	0.061	0.176	2.889	0.543	71.76	8.87	1.52	4.37	13.48	++++	4.06	No	½B
										b	890	1.016	5.199	0.429	0.023	0.191	4.066	0.490	78.21	8.25	0.44	3.67	9.43	+++	4.31		½B
357	35	F	7/16	9/1	7/16–8/16	Severe	39.000	42.15	Negative	a	600	1.027	5.845	0.403	0.107	0.277	4.287	0.671	75.06	6.90	1.83	4.74	11.47	++++	7.10	No	G
										b	1,275	1.022	10,690	0.508	0.049	0.219	9.206	0.708	86.12	4.75	0.46	2.05	6.65	++	5.20		G
371	75	F	8/ 8/17	4/12/18	7/27–10/11/17	Severe	39.550	45.15	Hyaline casts	a	515	1.019	3.918	0.236	0.084	0.201	2.843	0.554	72.56	6.02	2.14	5.14	14.14	++++	5.08	No	G
										b	1,010	1.024	11.964	0.585	0.077	0.253	10.131	0.918	84.68	4.89	0.65	2.11	7.67		5.60		B
372	44	M	8/ 8/18	4/19/18	8/8–10/11/17	Severe	62.860	69.75	Negative	a	1,015	1.018	5.033	0.344	0.134	0.392	4.169	0.000	82.83	6.83	2.66	7.79	0	++++	6.24	No	B
										b	1,390	1.020	14.779	0.774	0.166	0.427	10.956	2.456	74.13	5.24	1.12	2.89	16.62		6.12		B+⅛
379	28	F	8/15/17	9/30	8/15–9/27	Severe	43.550	45.95	Albumin	a	350	1.031	3.043	0.417	0.137	0.229	1.805	0.455	59.32	13.70	4.50	7.53	14.93	++	5.26	No	G
										b	1,555	1.020	11.751	0.738	0.103	0.279	10.069	0.562	85.69	6.28	0.88	2.37	4.78		6.07		G
381	42	M	8/20	9/3	8/20–8/31	Severe	48.780	49.15	Negative	a	1,370	1.013	5.221	0.394	0.099	0.140	3.893	0.695	74.56	7.55	1.90	3.34	13.31	++	2.87	No	G
										b	770	1.028	8.732	0.561	0.194	0.309	6.105	1.563	69.92	6.42	2.22	3.54	17.90		6.29		G
384	22	F	8/27	10/16	9/ 5–10/11	Severe	40.950	46.15	Granular casts	a	1,070	1.013	5.558	0.372	0.055	0.232	4.290	0.609	77.19	6.69	0.99	4.17	16.96	+	5.67	No	B
										b	1,460	1.014	11.053	0.652	0.124	0.285	9.081	0.911	82.16	5.90	1.12	2.58	8.24		6.18		B
386	34	F	8/27	9/9	8/27–9/ 6	Severe	41.780	41.15	Granular and hyaline casts	a	1,160	1.009	4.880	0.818	0.052	0.246	3.340	0.424	68.44	16.76	1.07	5.04	8.69	+	5.89	Yes	B
										b	1,695	1.014	10.228	0.532	0.075	0.253	8.436	0.932	82.48	5.20	0.73	2.47	9.12		6.15		B
400	28	F	9/21	11/10	9/21–10/11	Severe	31.350	33.35	Trace sugar	a	550	1.023	4.466	0.308	0.106	0.169	2.880	1.003	64.49	6.90	2.37	3.79	22.45	+++	5.39	No	B
										b	490	1.024	4.885	0.327	0.075	0.178	3.756	0.127	76.89	6.69	1.60	3.64	11.18	+	5.34		B
337	46	M	6/13	8/21	7/12–8/21	Moderate	69.147	72.35	Granular and hyaline casts	a	960	1.026	10.468	1.138	0.172	0.459	7.174	1.525	68.53	10.87	1.59	4.24	14.77	+++	6.64	No	G
										b	1,525	1.024	15.398	1.093	0.111	0.560	11.858	1.776	77.01	7.10	0.72	3.64	11.53	++	7.74		B+⅛
338	25	F	6/13	8/17	7/12–8/16	Moderate	37.952	40.15	Trace albumin, casts	a	630	1.026	7.480	1.039	0.131	0.220	4.741	1.349	63.38	13.89	1.73	2.90	18.10	+++	5.80	Yes	G
										b	1,610	1.020	12.808	0.712	0.112	0.238	10.586	1.160	82.65	5.56	0.87	1.86	9.06	++	5.93		B
347	25	F	6/27	8/9	7/12–8/ 7	Moderate	40.850	41.65	Negative	a	1,105	1.019	7.173	0.451	0.099	0.303	5.151	1.169	71.81	6.29	1.38	4.22	16.30	+ purple	7.42	No	G
										b	1,320	1.019	8.826	0.337	0.125	0.286	7.627	0.451	86.42	3.82	1.42	3.24	5.10		6.87		G
358	26	F	7/16	9/1	7/16–8/31	Moderate	43.743	45.95	Granular and hyaline casts	a	780	1.023	5.987	0.489	0.094	0.278	4.535	0.591	75.75	8.17	1.57	4.65	9.86	++	6.36	Yes	G
										b	1,520	1.021	9.278	0.515	0.163	0.365	7.432	0.803	80.10	5.55	1.42	3.93	8.66	++	7.94		G
378	29	F	8/13	8/28	8/13–8/22	Moderate	47.545	48.35	Slight albumin and hyaline casts	a	410	1.031	4.240	0.336	0.086	0.238	3.038	0.542	71.65	7.92	2.03	5.61	12.79	++	5.01	No	G
										b	1,240	1.022	9.031	0.656	0.121	0.393	7.293	0.569	80.75	7.26	1.34	4.35	6.30		8.13		G
385	44	F	8/27	9/19	8/27–9/13	Moderate	39.145	39.95	Trace sugar	a	1,040	1.017	6.602	0.355	0.099	0.174	4.690	1.284	71.04	5.38	1.50	2.64	19.44	++++	4.44	No	B
										b	1,000	1.019	9.226	0.493	0.129	0.188	8.109	0.307	87.89	5.34	1.40	2.04	3.33		4.71		B
388	36	M	8/28	9/23	8/27–9/20	Moderate	52.250	52.55	Granular casts	a	1,490	1.015	6.049	0.430	0.192	0.362	4.210	0.855	69.60	7.11	3.17	5.98	14.14	+	6.93	No	G
										b	1,580	1.017	8.171	0.575	0.141	0.422	5.873	1.160	71.88	7.04	1.72	5.16	14.20		8.03		G
285a	40	M	9/ 5	12/20	9/ 6–10/11	Moderate	49.545	50.85	Negative	a	2,155	1.008	7.905	0.676	0.082	0.321	6.367	0.459	80.54	8.55	1.04	4.06	5.81	+ slight	6.48	Yes	G
										b	1,560	1.018	14.305	0.809	0.147	0.348	12.031	0.970	84.10	5.66	1.03	2.43	6.78		6.84		B
395	24	F	9/10	11/ 3	9/10–10/4	Moderate	47.450	46.75	Negative	a	1,150	1.016	5.152	0.439	0.084	0.140	4.097	0.392	79.52	8.52	1.63	2.72	7.61	+	2.95	Yes	G
										b	1,195	1.017	9.244	0.488	0.094	0.189	8.125	0.348	87.89	5.28	1.02	2.04	3.77		4.04		B
396	31	F	9/11	10/ 6	9/11–10/4	Moderate	55.540	57.05	Granular and hyaline casts	a	820	1.024	5.889	0.262	0.101	0.174	4.944	0.408	83.95	4.45	1.72	2.96	6.92	+	3.13	No	G
										b	1,580	1.018	10.131	0.588	0.129	0.356	9.075	0.000	89.58	5.80	1.27	3.51	0.00		6.24		G
309	37	M	8/ 3	9/17	8/ 3–9/13	Mild	51.750	54.150	Negative	a	900	1.027	9.505	0.254	0.209	0.459	5.600	2.983	58.92	2.67	2.19	4.83	31.39	++	8.87	No	G
										b	1,410	1.019	9.890	0.647	0.129	0.442	8.305	0.367	83.97	6.54	1.30	4.47	3.72		8.16		G
370	57	M	8/ 6	10/ 1	8/ 6–9/27	Mild	51.945	54.445	Albumin	a	1,760	1.016	8.151	0.570	0.199	0.417	6.332	0.623	77.68	7.00	2.44	5.12	7.76	+ red	8.03	Slight	G
										b	1,220	1.019	9.758	0.655	0.099	0.331	7.951	0.752	81.48	6.71	0.68	3.42	7.71		6.08		B
375	47	M	8/ 9	10/13	8/10–8/31	Mild	56.350	56.750	Negative	a	1,400	1.019	8.499	0.855	0.229	0.474	5.582	1.359	65.68	10.06	2.69	5.58	15.99	+ slight	8.41	No	G
										b	1,850	1.017	13.572	0.725	0.140	0.476	11.021	1.210	81.20	5.34	1.03	3.51	8.92		8.39		B
387	33	M	8/27	10/13	8/27–10/11	Mild	50.575	52.350	Negative	a	1,180	1.020	7.004	0.368	0.093	0.348	5.826	0.369	83.18	5.25	1.33	4.97	5.27	+ slight	6.88	No	G
										b	1,265	1.022	10.484	0.488	0.143	0.362	8.934	0.557	85.22	4.65	1.36	3.45	5.32		6.92		G
389	43	M	8/28	10/14	8/28–10/11	Mild	51.050	53.150	Slight albumin	a	1,050	1.024	4.954	0.529	0.139	0.301	2.940	1.045	59.35	10.68	2.81	6.08	21.08	+	5.90	No	G
										b	1,150	1.023	14.098	0.609	0.166	0.376	11.891	1.056	84.35	4.32	1.18	2.67	7.48		7.07		G
390	36	F	9/ 2	10/ 5	9/ 3–10/4	Mild	53.200	53.350	Negative	a	1,965	1.018	7.950	0.891	0.173	0.332	5.483	1.071	68.97	11.21	2.18	4.18	13.46	+	6.24	Yes	G
										b	1,540	1.022	12.593	0.747	0.184	0.336	10.629	0.697	84.40	5.93	1.46	2.67	5.54		6.30		G
Average for severe cases							43.582	46.450		a	1,131	1.0176	4.857	0.441	0.084	0.225	3.418	0.599	71.739	9.175	1.901	4.874	12.986	+++	5.17		
										b	1,435	1.020	9.848	0.558	0.090	0.259	7.857	1.043	79.377	5.876	0.933	2.745	11.072		5.54		
Average for moderate cases							48.317	49.560		a	1,063	1.021	6.695	0.762	0.114	0.269	4.895	0.757	73.627	8.116	1.736	3.998	12.344	++	5.52		
										b	1,414	1.020	10.642	0.627	0.127	0.334	8.801	0.754	82.827	5.841	1.255	3.299	6.873		6.65		
Average for mild cases							52.478	54.033		a	1,376	1.021	7.669	0.678	0.174	0.389	5.292	1.244	68.963	7.812	2.270	5.127	15.825	+	7.39		
										b	1,406	1.020	11.733	0.645	0.139	0.389	9.789	0.773	83.873	5.582	1.170	3.395	6.352		7.15		
Average for all cases							47.460	49.397		a	1,158	1.020	6.214	0.519	0.116	0.279	4.457	0.844	71:81	8.453	1.92	4.60	13.48		5.82		
										b	1,420	1.020	10.588	0.605	0.115	0.318	8.665	0.870	81.64	5.79	1.12	3.07	8.39		6.34		

From July 13 to Sept. 13, 1917, inclusive, the urine was analyzed for each patient at entrance or shortly after entrance to the hospital and then at least twice a week. From Sept. 13, to Oct. 11, 1917, the urine was analyzed only once a week. The analyses included the determination of volume, specific gravity, total nitrogen, urea, ammonia, uric acid and creatinin, and the qualitative testing for indican and albumin of the twenty-four hour urine for all uncomplicated or little complicated cases in the hospital. The collected data are given in Table 5 with the cases arranged in groups according to the severity of the symptoms. The different items of the table may be dealt with separately at least in part.

VOLUME AND SPECIFIC GRAVITY

The average volume individually for the four normal individuals in fifty-seven tests from July 13 to October 11 was 1,176, 1,009, 759, 855 c.c., respectively, with a general average of 950 c.c. The corresponding specific gravities were 1.027, 1.032, 1.031, and 1.031, respectively, with a general average of 1.030. These data were gathered in warm weather, when the controls were perspiring freely in the warm laboratory. The average for the first two tests in July for the controls was 936 c.c. volume and 1.031 specific gravity. The average volume for the last tests for four normal persons working in the laboratory from August 22 to August 31 was 844 c.c. The averages for the first estimation of volume and specific gravity for twenty-six pellagra patients, when the patients were nearest the active pellagra period and the shortest time on a remedial diet, were 1,158 c.c. and 1.0196 respectively. These averages include a case of polyuria. Excluding this case, the average volume for the pellagra patients becomes 1.039 c.c., and the average specific gravity 1.020.

The average of the last determinations for the patients taken just before each patient was discharged or for a few patients a short time before discharge, at the time the patient was well on the road to convalescence and showed no outward sign of pellagra, was 1,420 c.c. for volume and 1.0196 for specific gravity. Excluding the case of polyuria of over 3,800 c c volume, the volume of the urine in the last determinations becomes 1,322 c.c. and the specific gravity 1.020.

Excluding the case with polyuria, nineteen out of twenty-five cases increased in volume of the urine in the hospital; seventeen increased in specific gravity; seven increased in both volume and specific gravity; two increased in specific gravity with little change in volume; and one increased considerably in volume with no change in specific gravity.

Of the cases studied, three classifications were made: those with intense extensive eruption or with considerable erythema and marked general malnutrition and general weakness were classed as severe cases;

those with considerable erythema and with but slight evidence of malnutrition and weakness were classed as moderate cases; those with mild skin symptoms and slight systemic involvement were classed as mild cases.

Excluding the case of polyuria in the estimation of volume, the severe cases have a much smaller volume (799 c.c.) than the moderate cases (1,053 c.c.) and these, in turn, less than the mild cases (1,376 c.c.).

The possibility that the increase in average volume of urine from the active pellagrous stage to the stage in which the signs and symptoms of pellagra have disappeared is tied up with a change in season or a temperature change with less sweating, is but a small part—a very small part—of the explanation of the change in volume. Thus, of seven cases (Cases 353, 357, 337, 347, 358, 378, 375) in the tests from July 12 to August 31, the increase in average volume from the first test to the last is from 831 c.c. to 1,374 c.c. Four normal persons, working in the laboratory, varied in that period from 936 average volume to 844 c.c.—a slight loss in fact. Five cases (Cases 341, 381, 285a, 370, 390, for the most part cases with large initial volume) decreased in volume from the first test to the last tests, during the period from July 12 to October 11. Several cases (Cases 400, 385, 395) were practically constant in volume in the first and last tests. For Case 338, the cessation of the diarrhea would explain in part, at least, the increase in volume in the convalescent stage. The change in volume between the first and last tests in the hospital would thus seem to be tied up with a greater or less return of the patients to the average volume that would normally obtain for them on a diet such as they had at the hospital and a similar mode of living. This conclusion is strengthened by the fact that the average for all types of cases, severe, moderate and mild in the last analyses is approximately 1,400 c.c.

The increased volume of the urine of the convalescent cases in the hospital may be due: (1) to a change in the consistency of the feces (what few batches of feces we had occasion to examine were, in the active stage of the disease, rather bulky and soft with apparently a high water content); (2) to greater intake of food with a resultant greater intake of fluid, and (3) to the greater intake of water as such to aid in the excretion of the greater nitrogenous waste as found in the urine in the convalescent stage. As to the volume of the urine in pellagra, Marie[19] states: "Of 100 pellagra patients, the quantity of urine in twenty-four hours showed an average of 900 c.c. with a minimum of 500 c.c., and a maximum of 1,900 c.c. The quantity is, therefore, less

19. Marie: Pellagra. Translated by Lavinder and Babcock, Columbia, S. C., 1910, p. 215.

than normal. Calderni also found in 35 per cent. of his pellagra patients a great diminution of the quantity of urine."

Whatever may be the reason, therefore, the fact remains that for the pellagrins studied at the pellagra hospital in 1917 there is predominantly a decrease in the volume of the twenty-four hour urine in the pellagrous period as compared with the stage when the signs and symptoms have disappeared.

TOTAL NITROGEN

The elimination of total nitrogen, as shown by the tests made as soon as possible after the patient had been admitted to the hospital, was very much below that of normal persons.

The total nitrogen of the urine of twenty-six cases (Cases 337 to 400) in the first tests made, including analyses made in one case (Case 371) of the twenty-four hour urine collected in the home one week before admission to the hospital varied from 3.043 to 10.468 gm., with an average of 6.214 gm. The total nitrogen of the urine in the first test after admission to the hospital with at least one day on the hospital diet varied from 3.043 to 10.468 gm., with an average of 6.257 gm. When divided according to the severity of symptoms, the average total nitrogen of ten severe cases at the first test made on or very shortly after entrance to the hospital was 4.857 gm.; of ten moderate cases 6.695 gm.; and of 6 mild cases 7.669 gm. The total nitrogen for the last estimation before discharge varied from 5.199 in Case 353 (with some mental symptoms and a finicky appetite) to 15.398 gm., with an average of 10.588 gm. Leaving out this case in the last estimation, the average total nitrogen of the urine of the cured patients becomes 10.804 gm. Here, again, the total nitrogen of the urine of 10 severe cases (9.848 gm.) is lower than that of the moderate cases (10.642 gm.) and the mild cases (11.733 gm).

AMMONIA, UREA, URIC ACID, CREATININ

Total nitrogen of the urine collected shortly after the patient had entered the hospital is on the average, as shown, low (6.214 gm.). The urine likewise shows a low absolute content of ammonia nitrogen (0.519 gm.); a low uric acid (0.116 gm.); a low creatinin nitrogen (0.279 gm.); a low urea nitrogen (4.457 gm.). The ratio of urea nitrogen to total nitrogen is low (71.81); the ammonia ratio is high (8.453); the creatinin ratio slightly high (4.60); the undetermined nitrogen ratio high (13.48); the creatinin coefficient low (5.82). The low ratio of urea nitrogen to total nitrogen and the heightened ammonia ratio are in accord with the findings of Camurri, while the data, as a whole, are an accentuation of the findings of Myers and Fine.

In the case of the urine of the same patient about to be discharged, or well along in the convalescent stage with no outward manifestation of pellagra and with a heightened joy of living and sense of well being, the total nitrogen and urea are much increased; the urea ratio is much greater; the ammonia ratio is much reduced; and the ratio of undetermined nitrogen is much reduced.

When the patients are divided into groups according to the severity of the symptoms, extent and vividness of the erythema and general weakness and malnutrition with more or less skin symptoms, it may be seen from Table 5 that the severe cases have a smaller value for volume (excluding a case of polyuria) specific gravity, total nitrogen, ammonia nitrogen, uric acid nitrogen and urea, and for the creatinin coefficient than the moderate cases and the moderate cases less than the mild cases. On the other hand, the severe cases have a higher ratio of ammonia nitrogen to total nitrogen than the moderate cases and these, in turn, have a higher ratio than the mild cases.

Bearing in mind the results of the urinary analyses made shortly after the patient had entered the hospital, it becomes of interest to compare the results of Table 5 (a) with the data given by Folin on different diets of low and high protein.

Folin [20] shows that urine obtained from normal persons does not necessarily exhibit any such constancy in composition as has been supposed to be the case. Quantitative changes in the daily protein catabolism are accompanied by pronounced changes in the distribution of the urinary nitrogen and sulphur and the variations occur according to laws that can be formulated with a fair degree of precision. The nature of these variations may be expressed by the following generalizations.

"1. *Creatinin.*—The absolute quantity eliminated in urine on a meat-free diet is a constant quantity different for different individuals but wholly independent of quantitative changes in the total amount of nitrogen eliminated.

"2. *Uric Acid.*—When the total amount of protein metabolism is greatly reduced the absolute quantity of uric acid is diminished but not nearly in proportion to the diminution in the total nitrogen and the per cent. of uric acid in terms of the total is therefore much increased.

"3. *Ammonia.*—With pronounced diminution in the protein metabolism as shown by the total nitrogen in the urine there is usually but not always and therefore not necessarily a decrease in the absolute quantity of ammonia eliminated. A pronounced reduction of the total nitrogen is, however, always accompanied by a relative increase in the

20. Folin: Laws Governing the Chemical Composition of Urine, Am. J. Physiol. **13**:67, 1905.

ammonia nitrogen, provided that the food is not such as to yield an alkaline ash.

"4. *Urea.*—With every decided diminution in the quantity of total nitrogen eliminated there is a propronounced reduction in the per cent. of that nitrogen represented by urea. When the daily nitrogen has been reduced to about 3 or 4 gm., about 60 per cent. of it only is in the form of urea."

The picture afforded by the results of urinary analysis in the active pellagra stage of the hospital patients of 1917 is that of malnutrition and low protein metabolism with low total nitrogen elimination; with, in general, a lowered ammonia elimination, though a few have an absolute increase in ammonia elimination; with, in general, a heightened ratio of ammonia nitrogen to total nitrogen; with the uric acid somewhat diminished but not in proportion to the total nitrogen; with a low creatinin but with little variation with change in the total nitrogen from the pellagrous to the convalescent stage; with low urea and a low ratio of urea nitrogen to total nitrogen. It may be pointed out that the urea ratio in some cases with not very low total nitrogen (Cases 337, 338, 369 and 375), is much lower than would be expected. Thus, the average total nitrogen of these four cases is 9.238 gm., the average urea ratio only 64.13.

The constituents dependent on exogenous factors, urea and ammonia, are in agreement with the protein catabolism, those of endogenous origin, uric acid and creatinin, are, in general, in harmony with the poor physical condition of the patients, low vitality and more or less atrophy of muscle.

The uric acid elimination, on the average, differs very little in the active stage from that of the convalescent patients. The creatinin elimination remains low, as shown by the creatinin coefficient, which averages 5.17 for the acute stage of the severe cases and 5.54 for the same patients about to be discharged; 5.52 for the moderate cases and 6.65 for the same patients about to be discharged; 7.39 and 7.15 for the corresponding periods in the case of the mild attacks. The creatinin coefficient of the patients with a mild attack of pellagra is comparable with that of normal persons, which varies from 7 to 11.

The severity of attacks of pellagra may be differentiated primarily by the extent and intensity of the eruption and secondly by the eruption, general malnutrition, and subjective symptoms. Goldberger, Wheeler, and Sydenstricker [21] suggest "the possibility if not the probability that pellagra includes at least two commonly associated but etiologically essentially distinct though closely related syndromes, namely: (1) the

21. Goldberger, Wheeler and Sydenstricker: J. A. M. A. **71**:944 (Sept. 21) 1918.

syndrome that is comprehended by the phrase "pellagra sine pellagra," and (2) "the dermatitis or pellegra without or with only slight subjective manifestation." Of the hospital patients considered in the present report, at least two rough classifications can be made, (1) those with marked skin symptoms but otherwise not much physical deterioration, a class which may be called dermal; (2) those with moderate or slight skin symptoms but with general weakness, paresthesia, and marked intestinal upset, a class which may be called systemic. The differentiation into classes is more noticeable in the severe cases.

Dividing the severe cases into these groups as shown in Table 6, it may be seen that the total nitrogen, urea nitrogen and creatinin nitrogen of the systemic group are lower than those of the dermal group, and that the ratio of the urea nitrogen to total nitrogen is lower for the systemic group, that the creatinin coefficient is lower, the undetermined nitrogen and the ratio of undetermined nitrogen to total nitrogen is higher. The biochemical study, therefore, offers support for the view of Goldberger, Wheeler, and Sydenstricker as to distinct syndromes.

TABLE 6.—URINARY DATA IN PELLAGRA IN RELATION TO DOMINANCE OF MANIFESTATIONS

Manifestations Dominant	Total Nitrogen	Urea Nitrogen	NH_3N N	Creatinin N	Undetermined N	Ratio Urea N Total N	Ratio NH_3N Total N	Undetermined N Total N	Creatinin Coefficient	Casts and Albumin
Dermal:										
Case 341.....	6.576	4.681	0.758	0.186	0.949	71.18	11.53	14.43	4.17	Negative
Case 357.....	5.845	4.387	0.403	0.277	0.671	75.06	6.90	11.47	7.10	Negative
Case 372.....	5.063	4.169	0.344	0.392	0.000	82.83	6.83	0.00	6.24	Negative
Case 384.....	5.558	4.290	0.372	0.232	0.609	77.19	6.69	16.96	5.67	Granular casts
Average....	5.753	4.382	0.469	0.272	0.557	76.57	7.99	10.72	5.80	
Systemic:										
Case 352.....	4.026	2.869	0.357	0.176	0.543	71.76	8.87	13.48	4.06	Albumin
Case 371.....	3.918	2.843	0.236	0.201	0.554	72.56	6.02	14.14	5.08	Hyaline casts
Case 379.....	3.043	1.805	0.417	0.229	0.455	59.32	13.70	14.93	5.26	Albumin
Case 381.....	5.221	3.898	0.394	0.140	0.695	74.56	7.55	13.31	2.87	Negative
Case 386.....	4.880	3.340	0.818	0.245	0.424	68.44	16.76	8.69	5.80	Granular and hyaline casts
Case 400.....	4.466	2.880	0.308	0.169	1.003	64.49	6.90	22.45	5.39	Trace sugar
Average....	4.259	2.942	0.422	0.194	0.612	68.52	9.97	14.50	4.76	

FOOD UTILIZATION IN PELLAGRA

The data gathered in Table 5 (*a*) show the picture of a low protein metabolism. This conclusion brings up the question of food utilization in pellagra, especially the utilization of protein. Including the preliminary period, June 22 to July 13, the total nitrogen of the food consumed during the time the first twenty-four hour urine was being collected varied (as given in Table 7) from 7.134 to 16.571 gm. with an average of 11.388 gm. One week later, the average quantity of food consumed by each individual for the day the urine was being collected and the day

previous, varied from 7.775 to 16.594 gm. with a general average of 12.748 gm. The body weight at the outset of the urine study varied from 39 kg. for an adult female to 68.745 kg. for a strongly built male, with an average of 47.51 kg. The appetite of the patients who had just entered the hospital was, in general, fair, the quantity of food eaten and the nitrogen thereof was not excessively low. However, the nitrogen excreted in the urine, with little gain in weight, remained low for several weeks, as shown in Table 7. It is not uncommon, in fact, to find a slight loss or no gain in weight during the first week or two of residence in the hospital. It would seem that the ability to assimilate food is low in pellagra, that the power to utilize food is in general only slowly regained.

Myers and Fine,[4] working in cooperation with the Thompson-McFadden Commission, conclude from their results on metabolism studies of pellagrins that the ability of the pellagrins to absorb their food is only slightly, if at all, impaired, and that whatever impairment there was is, in part, due to diarrhea. Myers and Fine's cases, as judged by their case histories, were for the most part mild cases at the time experimental work began.

Hunter, Givens and Lewis[5] studied nitrogen balances on seven patients at the Pellagra Hospital, Spartanburg, S. C., in 1914. Two of these patients (Cases 2 and 14) had been on a highly nourishing remedial diet for twenty-six and eighteen days, respectively, before the metabolism study was started. One of these at entrance was a mild case, the other was a severe case. The utilization of protein by these cases was, respectively, practically 93 and 88 per cent. The five other cases studied by Hunter, Given and Lewis for nitrogen balances (Experiments 3 to 7, Cases 1, 19, 36, 46 and 32) were on a low protein vegetable diet, somewhat comparable to a pellagra producing diet. These five cases showed a low protein utilization. Thus, Case 1 showed a protein utilization varying from 76 to 85; Case 19, from 60 to 67 per cent.; Case 36 over the whole period of twenty-three days had a protein utilization of only 71.5 and for the first period of eight days, the period of best utilization, only 77.2 per cent.; Case 46 over the whole period of study of twenty-seven days had a protein utilization of 81.5 per cent.; Case 32, described as a mild case, was for seven days on the vegetable diet, for a second period of nine days on a modified vegetable diet, and for seven days on a diet containing a high content of animal protein in the form of meat and eggs. During the first two periods, the nitrogen balances were negative and the protein utilization was low, 73.5 per cent.; during the last period on a high protein diet the utilization was 87.5 per cent.

It would seem, therefore, that on a low protein vegetable diet the utilization of protein by active pellagrins is low and that, as shown in

TABLE 7.—Data on Relation of Nitrogen Intake and Excretion to Weight

Case	Date of First Analysis in Hospital	Nitrogen of the Urine, Gm.			Nitrogen of the Food Eaten, Gm.			Body Weight, Kg.			Nitrogen of Urine and of Food and Body Weight at End of Experiment			Date of Last Urine Tests	Last Weight in Hospital	
		First Analysis	Second Analysis, 1 Week Later	Third Analysis, 2 Weeks Later	First Analysis	Second Analysis	Third Analysis	First Analysis	Second Analysis	Third Analysis	Urine,* Gm.	Food, Gm.	Body Weight, Kg.		Weight, Gm.	Date of Last Weighing
337	6/23/17	8.44	7.210	9.780	11.825	14.535	16.599	68.745	68.850	69.550	15.398	19.022	72.35	8/21	72.35	8/18/17
338	6/23/17	4.782	7.002	8.395	7.735	12.979	13.623	39.55	40.154	38.760	12.808	16.625	40.15	8/16	40.15	8/11/17
341	6/28/17	5.936	5.479	6.576	8.542	14.751	16.604	44.154	43.150	44.650	13.525	16.604	47.35	8/22	47.75	8/25/17
347	7/ 5/17	5.590	7.173	7.947	8.261	11.002	11.291	39.948	40.850	41.035	8.826	12.168	41.65	8/ 7	41.65	8/ 4/17
353	7/20/17	4.139	4.026	2.924	7.134	7.775	9.273	44.535	43.350	43.750	5.199	9.738	44.35	8/16	44.35	8/18/17
357	7/17/17	5.845	6.130	9.530	12.807	12.846	13.198	39.00	40.035	40.550	10.600	16.579	42.15	8/16	44.35	9/ 1/17
358	7/17/17	5.987	7.210	7.150	8.613	8.611	12.927	43.743	43.035	43.150	9.278	12.968	45.95	8/31	45.95	9/ 1/17
369	8/ 4/17	9.505	7.727	9.156	10.800	12.879	12.918	51.75	52.750	53.150	9.890	12.958	54.15	9/13	54.15	9/15/17
370	8/ 7/17	8.151	7.321	9.410	13.179	16.594	16.580	51.945	50.250	49.950	9.758	16.580	54.445	9/27	54.445	9/29/17
371	8/10/17	5.630	9.450	10.885	8.671	10.980	14.813	39.55	40.250	39.550	11.964	15.236	45.15	10/11	55.35	4/ 6/18
372	8/ 9/17	5.083	13.785	11.313	16.517	16.580	16.571	62.86	63.250	63.950	14.779	19.793	69.75	10/11	79.561	4/13/18
375	8/11/17	8.499	11.860	14.578	13.063	12.936	16.661	56.350	55.350	55.750	13.572	16.580	56.75	8/31	59.65	10/13/17
378†	8/14/17	4.240	8.190	.....	11.144	10.454	.....	47.545	48.350	.....	9.031	12.595	48.35	8/22	49.15	8/25/17
379	8/16/17	3.043	6.474	8.163	12.119	11.589	12.955	43.55	44.450	44.550	11.751	12.997	46.75	9/27	46.75	9/29/17
381†	8/21/17	5.221	8.732	.....	12.957	11.924	.....	48.780	49.150	.....	8.732	11.924	49.15	8/31	49.15	9/ 1/17
384	8/29/17	3.095	5.558	9.115	9.792	11.413	14.702	41.355	40.950	42.350	11.053	16.089	46.15	10/11	46.15	10/13/17
385	8/28/17	6.602	10.636	9.226	11.874	15.064	14.430	39.145	39.660	39.950	9.226	14.430	39.95	9/13	39.95	9/15/17
386†	8/28/17	4.880	10.228	.....	14.599	16.548	.....	41.780	41.150	.....	10.228	16.580	41.15	9/ 6	41.15	9/ 8/17
387	8/28/17	7.004	8.528	8.453	13.092	12.949	12.951	50.575	49.750	50.350	10.484	13.846	52.35	10/11	52.35	10/13/17
388	8/29/17	6.049	8.074	7.859	13.954	12.951	12.952	52.250	51.750	52.150	8.171	12.952	52.55	9/20	52.55	9/22/17
389	8/29/17	4.954	8.487	9.089	12.944	12.951	12.952	51.050	49.950	50.150	14.098	16.541	53.15	10.11	53.15	10/13/17
390	9/ 4/17	7.950	8.658	10.075	12.790	12.957	15.328	53.2	51.350	52.550	12.593	15.066	53.35	10/ 4	53.35	9/29/17
285a	9/ 7/17	7.906	9.818	12.903	12.952	12.952	16.617	49.545	49.350	49.350	14.305	16.546	50.85	10/11	54.35	12/15/17
395	9/11/17	5.152	8.140	10.293	7.687	14.120	13.871	47.450	45.750	46.845	9.244	16.546	46.75	10/ 4	49.35	11/30/17
396	9/12/17	5.889	9.225	11.606	12.952	12.972	13.547	55.540	56.250	57.150	10.131	13.610	57.05	10/ 4	57.05	10/ 6/17
400	9/23/17	4.466	6.391	5.602	10.110	10.072	14.669	31.350	32.350	32.550	4.885	10.360	33.35	10/11	34.75	11/10/17
Average.....		5.923	8.135	9.132	11.388	12.748	14.176	47.509	47.364	47.902	10.755	14.805	49.453	.....	50.727	

* The nitrogen of the urine and of the food, and the body weight is not necessarily the same as given in the last test of Table 5 since the complete analysis of the urine of Table 5 stopped in some instances before the last analysis of the urine for total nitrogen.

† Left the hospital after little improvement contrary to advice. Excluding these cases (378, 381, 386) the average weight at entrance becomes 47.702 kg., at discharge 51.281 kg.

Case 32 of Hunter, Givens and Lewis' study, the utilization of the protein of a high animal protein diet was 87.5 per cent. when determined immediately after the change from low protein to a high protein diet.

Wilson and Roaf [22] carried out a partial metabolism experiment on two groups of men in Egypt; a group of five healthy men and a similar group of five pellagrins said to be in the convalescent stage. They found the loss of nitrogen in the feces was "35 per cent. in the pellagrins, and 33 per cent. in the healthy men, a difference of 6 per cent."

In our work it was found that with no gain in weight on the average, with a good intake of nitrogen, the nitrogen of the urine in the early days of the patient's stay in the hospital was small. These findings implied that the utilization of protein was low. Accordingly, a group of patients was selected for a study of the nitrogen balance for a three-day period, July 31 to August 2, inclusive. The results are given in Table 8. The protein utilization varied from 73.9 per cent. for a severe case, a patient who had been on hospital diet G for fifteen days, to 92.6 for a severe case in which hospital diet B was given for thirty-seven days, with an average for the six patients of 84.5. It is now our belief that we worked with patients well on the way to convalescence, and that if we had tested patients in the first few days of their residence in the hospital, the protein utilization would have been smaller. In passing, it might be said that in three or four weeks on a diet rich in milk, meat, and eggs, etc., the patients greatly improve in well being, in the joy of living, and that in addition the skin symptoms show marked amelioration.

TABLE 8.—Protein Utilization in Pellagra

Case	Nitrogen of Food	Nitrogen of Urine	Nitrogen of Feces*	Nitrogen of Urine and Fecal Nitrogen	Nitrogen Balance	Percentage Utilization of Protein	Diet	Days on Diet Before Utilization Test	Diarrhea
337	19.197	13.486	3.513	16.999	2.198	81.7	B+⅓	48	No
338	16.604	10.930	1.505	12.455	4.169	90.9	B	48	No
341	16.004	8.458	1.236	9.694	6.910	92.6	B	31	No
347	12.311	9.444	1.848	11.292	1.019	85.0	G	34	No
357	12.992	8.727	3.391	12.118	0.874	73.9	G	15	No
358	12.812	7.711	2.233	9.944	2.868	82.6	G	15	Slight
Aver.	15.087	9.796	2.288	12.084	3.006	84.5	..	32	

* Carmin was used as a marker. The nitrogen was determined on the fresh sample.

The facts on protein utilization as marshalled by us are: (1) patients who had been on a remedial diet for at least fifteen days before the protein utilization tests were made showed a utilization varying from 73.9 to 92.6 per cent., with an average of 84.5 per cent.; (2) in the

22. Wilson and Roaf: Report of a Committee Regarding Prevalence of Pellagra Among Turkish Prisoners of War, 1919. Appendix 8, p. 57.

first analysis after entrance to the hospital and one week later the average nitrogen of the urine was only 5.923 and 8.135 gm., respectively, while the average nitrogen of the food eaten was 11.388 and 12.748 gm., respectively; (3) that notwithstanding a good intake of food, there was no gain in weight in the first week in the hospital. Taking all these data together, we should judge that the utiliization of protein by persons suffering with marked pellagra tends to be somewhat subnormal.[23]

QUALITATIVE TESTS

Indican.—Indican [24] as determined by Obermayer's reagent and extraction with chloroform was positive in the urine of all patients. The occurrence of indican in the urine has been reported by a number of investigators. In our work, the indican reaction was much stronger for the severe cases than for the moderate or mild cases. No great stress was put on indican in the urine as a symptomatic mark in pellagra, however, for as well shown by Hunter, Givens and Lewis, pellagra is compatible with any degree whatever of indican production even with none at all and Goldberger and Wheeler found little, if any, indican in the urine of their volunteers on a mainly cereal diet by means of which they experimentally produced pellagra in previously healthy normal persons. Further, following the lead of Myers and Fine who found increased amounts of indol and skatol in the feces of pellagrins, several cases were noted in which the feces would give strong qualitative tests for indol and skatol with little indican in the urine. Baumstark [25] claims that *indol formation in the intestine and the excretion of indoxyl do not run parallel.*

All the patients tested showed indican in the urine, some strikingly. The indican must arise from more or less putrefaction in the intestine due to a varying degree of nonutilization of protein, to slow assimilation of protein fission products such as tryptophan, to a varying degree of retention of feces, and an active putrefactive flora.

Unknown Substances.—Ehrlich's diazo reaction [26] and Russo's methylene blue reaction [26] were positive in the urines of many of the hospital patients.

23. Some investigators of pellagra believed that once a pellagrin always a pellagrin. This view is no longer tenable. Despite the fact that in many cases the gastric juice is more or less deficient in hydrochloric acid even in the cases as discharged from the hospital, the general condition, activity, and appearance of the discharged patients as a whole would put them in the normal class, a class they would remain in as far as pellagra is concerned as long as the proper diet and normal modes of living are adhered to.

24. Most of the indican tests were made by Assistant Surgeon C. H. Waring of the medical staff.

25. Baumstark: München. med. Wchnschr. **1**:722, 1903.

26. See Hawk's Practical Physiological Chemistry, Ed. 5, Philadelphia, P. Blakiston Sons Co., pp. 454, 455, 1917.

Physiologic Bases.—Taking the high indican and the diazo reaction of the urine, and the presence of skatol and indol in the feces, as suggestive of an abnormal protein metabolism, large batches of the patients' urine were tested for physiologic bases. The bases sought for were beta-iminazolyl-ethylamine ($C_5H_9N_3$) which Ackermann [27] found to be produced from histidin by the action of putrefactive bacteria and obtained from the intestinal mucosa by Barger and Dale [28]; indolethylamin ($C_{10}H_{42}N_2$) obtained by Ewins and Laidlaw [29]; parahydroxyphenyl-ethylamine from tyrosin as shown by Barger and Walpole [30]; the diamins, putrescin and cadaverin. Using accepted methods, various types of basic material were isolated from the pellagrous urines but not in large enough amounts to be satisfactorily identified.

Albumin and Casts.—Evidence of kidney abnormalities in pellagra has been previously reported.[31] In the Illinois investigation, degenerative changes were found in the renal epithelium with more or less interstitial nephritis. Myers and Fine found granular and hyalin casts in the urine of a number of cases. In our work little evidence of kidney change was noted for the mild cases. Of the severe and moderate cases, about 50 per cent. gave evidence of kidney abnormalities as witnessed by the presence of albumin and casts in the urine.[32] However, as shown in Table 5, there can be marked cases of pellagra with no evidence whatever of kidney change.

SUMMARY

The study of the urine in pellagra at the U. S. Pellagra Hospital in 1917 may be summarized as follows:

1. The mineral metabolism seemed to be abnormal especially in the actively pellagrous stage as witnessed by the low P_2O_5 excretion despite the fact that the diet taken at the time was a generous one with abundance of milk.

2. Indications were present of a heightened putrefactive process in the intestines.

3. The presence of casts or albumin or both casts and albumin in the urine gave evidence of more or less kidney change in about 50 per cent. of the cases. Marked pellagra can occur with no evidence of kidney change.

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27. Ackermann: Ztschr. f. physiol. Chem. **64**:504, 1910.
28. Barger and Dale: J. Physiol. **41**:499, 1911.
29. Ewins and Laidlaw: Proc. Chem. Soc. **26**:343, 1910.
30. Barger and Walpole: J. Physiol. **38**:343, 1909.
31. Pellagra in Illinois. Condensed Report of the Illinois Pellagra Commission, Arch. Int. Med. **10**:123, 219 (July-Aug.) 1912.
32. The evidence regarding casts in the urine was taken from the clinical records made by Assistant Surgeon C. H. Waring.

4. There was low excretion of total nitrogen and the ordinary urinary ingredients.

5. The urea ratio, in general, was low, and in certain cases with fair total nitrogen the urea ratio was lower than should be expected—a finding which suggests liver insufficiency.

6. There was a heightened ratio for ammonia nitrogen and undetermined nitrogen.

7. The metabolic level during the active stage of the disease was low as further shown by the low excretion of uric acid and creatinin.

8. The creatinin coefficient was much below normal.

9. The utilization of protein was found to be subnormal, even after several weeks of a remedial diet.

10. With at least a month on the curative diet, the urinary ingredients rose to approximately normal amounts, the urea ratio rose to normal and the ammonia ratio fell to normal.

11. As suggested by Goldberger, Wheeler and Sydenstricker, the disease may be differentiated into at least two types: (1) a type with marked skin symptoms but with little physical degeneration; and (2) a type with slight skin symptoms but with profound systemic involvement. The abnormality in the urinary findings was greater for the systemic type than for the dermal type.

HEMOCHROMATOSIS

REPORT OF FOUR CASES *

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Hemochromatosis is a chronic disease of males occurring during middle life. Abbott [1] has reported one authentic case in a woman. It is characterized by (1) a pigmentation of the skin that varies from yellow to ashen gray and involves by preference the exposed parts, the axillae, and the genitals; (2) cirrhosis of the liver with moderate enlargement; (3) slight enlargement of the spleen; (4) fibrosis of the pancreas and lymph nodes; (5) hyperglycemia with or without glycosuria.

It is not a common disease. There are records of but four cases of genuine hemochromatosis among 5,000 recent necropsies in Bellevue Hospital. Fuchter [2] found only three instances of this disease in the clinical records of the Johns Hopkins Hospital, covering 106,000 admissions.

Clinically, hemochromatosis may easily be confused with other diseases attended by pigmentation of the skin. The pigment may not be visible. It may be late in its occurrence. It is very frequently a postmortem revelation. During life the only certain method of diagnosis is the microscopic demonstration of iron reacting pigment in the skin.

Pathogenesis of the Disease.—The chief interest in this disease centers around the remarkable and widespread pigmentation that occurs. In fact, if we could lose sight of the presence of this pigment altogether, the pathology of the disease would narrow itself down to that of an ordinary cirrhosis of the liver, spleen and pancreas, accompanied by clinical evidence of diabetes in a greater proportion of cases than we are accustomed to find in simple interstitial lesions of the pancreas.

The origin of the pigment has been variously ascribed to: (1) increased iron ingestion; (2) increased iron absorption; (3) decreased iron output (*a*, inability of the intestines and kidneys to put out iron; *b*, inability of the iron containing cells anywhere in the body to part with their iron); (4) fragility of the iron conveyors (erythrocytes), and (5) specific derangement of the organs that have to do with iron metabolism (liver and spleen).

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* From the Pathological Laboratory of the Bellevue Hospital, New York.

1. Abbott: Pig. Cirrhosis in a Case of Hemochromatosis, P. Path. & Bact., 755, 1901.

2. Futcher: Hemochromatosis with Diabetes, Am. J. M. Sc., **133**:78, 1907.

Nature of the Pigment.—1. Hemosiderin: This pigment is distinguished by the fact that it contains iron. Its exact chemical formula is as yet undetermined. It is easily demonstrated by Perl's method, appearing in the form of coarse Prussian blue granules. It is the more important pigment in hemochromatosis. The liver in a marked case of hemochromatosis is literally overrun with it, quantitative chemical determinations showing as much as one hundred times the normal amount of iron.

2. Hemofuchsin: This is an iron-free pigment that does not give Perl's reaction. The formula is not known. It occurs as fine light brown granules. It is never present in great amounts, and, indeed, its very existence has been disputed by Abbott, Beattie and others,[3] their contention being that, due to age, the iron is more firmly bound than in ordinary circumstances, and that by the use of hot reagents and a greater amount of time, the so-called hemofuchsin may be shown to contain iron. In carrying out this test, the frequency with which one encounters green and greenish blue reactions is supposed to add weight to this contention, especially in view of the fact that such green reactions can be turned into the typical Prussian blue reactions by using hot hydrochloric acid and giving the reaction sufficient time. We are inclined to believe that when the proper technic is observed, most, if not all, of the pigment can be shown to contain iron.

Distribution of the Pigment.—The organs in which pigment containing iron has been found are numerous. They include the liver, pancreas, lymph nodes, spleen, heart, suprarenals, thyroid, hypophysis, prostate and skin. Small amounts of such pigment occur also in the wall of the gastro-intestinal tract, in the testes, kidneys and bone marrow. The central nervous system and the lungs are comparatively free from it. The great mass of the iron pigment is found in the liver, pancreas and abdominal lymph nodes. Where the pigment occurs in such masses it is both extracellular and intracellular. Usually in those organs in which this extracellular pigment (overflow pigment) occurs we find scarring and connective tissue overgrowth. Since the two processes run parri passu, the indication is that they are related. Confirmatory of this is the fact that while great quantities of pigment are sometimes present in the heart, thyroid, suprarenals and hypophysis, it is entirely within the cells and is unaccompanied by fibrous change.

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3. Beattie: Hemochromatosis with Diabetes, J. Path. & Bact., **9**:117, 1903. Hess and Zurhelle: Clin. u. Path. Anatom. d. Bronz Diabetes, Ztschr. f. klin. Med., **62**:344, 1905. Heller: Skin Changes in Bronze Diabetes, Deutsch. med. Wchnschr., **30**:1716, 1907. Simmonds: Bronze Diabetes and Pig. Cirrhosis, Berl. klin. Wchnschr., **46**:531, 1909. Berg: Bronze Diabetes, Med. Rec., **56**: 117, 1899.

The site of election of this pigment is apparently the actively functioning cells of the parenchymatous organs. It occurs also in the endothelial cells of the blood vessels and ducts, in the heart muscle cells, and in Kupfer's cells in the liver. The connective tissue cells are also rich in hemosiderin in such organs as the liver and pancreas, but, as Sprunt [4] points out, this is probably secondary to the disruption of the overladen cells of the parenchymatous organs. The presence of hemosiderin in the connective tissue cells is never seen in such organs as the thyroid, suprarenals and hypophysis, though there may be great quantities of pigment, there is, nevertheless, no evidence of extensive cell destruction.

The pigment which, in the hands of certain workers, has failed to stain blue with the potassium-nitroprussid-hydrochloric acid reaction, the so-called hemofuchsin, is never a very prominent feature of the microscopic picture. It is described as fine light brown granules occurring in smooth muscle cells and also in the connective tissue cells.

Theories Explaining the Presence of Pigment.—Of purely theoretical interest is the idea which has been advanced that there may be an increase of ingested iron in the diet. Likewise, there is no proof of an increase in the known constant iron absorption which characterizes normal metabolism.

Turning to the question of whether there is a decreased iron output, we have first to consider a block in those excretory organs which are known to excrete iron. MacCallum [5] has suggested that the fault may lie in the intestines, the specific cells of iron excretion having lost that function. The kidney might likewise share in the iron block. Histological evidence is against such a view, because if such a sievelike action was operative, the iron would be expected to accumulate at the point of obstruction. As a matter of fact, the kidney and intestines in hemochromatosis are relatively poor in iron. In a case of bronze diabetes, Garrod was unable to detect any iron in the urine, stools or bile.

Iron is known to be widely present under normal conditions in the tissues. It enters into the chemical equation of all nucleoproteins, which are essential constituents of all cells. All cells of the body normally, therefore, have a part in iron metabolism, though in some organs they participate more actively than in others. This may be spoken of as a part of their chromogenic function. This fact, taken in conjunction with the known pathologic anatomy, i. e., of a widespread distribution of iron pigment in the cells, gives the basis of the theory

4. Sprunt: Hemochromatosis, Arch. Int. Med., **8**:75 (July) 1911.
5. MacCallum: A Textbook of Pathology.

advanced by Sprunt,[4] Parker,[6] Beattie,[3] and others, that some unknown agent injures the cell in such a way as to interfere with or destroy its iron metabolizing or chromogenic function. The cells which formerly metabolized their iron in a normal manner now become depots for its deposit, the machinery for moving it having in some way been injured or destroyed. This is somewhat analogous to the familiar observation of fat accumulation in injured cells.

The erythrocytes are known conveyers of iron in their hemoglobin. The great majority of the earlier writers assumed that excessive destruction of red blood corpuscles was the source of the accumulated iron. This idea was advanced by Von Recklinghausen[7] in his original description of the disease, and has since had the support of such authors as Osler, Abbott,[1] Opie,[8] Marie, Anschütz[9] and others.

Doubt of the validity of this argument is aroused by the fact that there is no anemia associated with hemochromatosis; that the red blood corpuscles are normal in appearance, and to fragility tests, and that spectroscopic examination of the blood serum shows normal hemoglobin. At the same time, there is no reactive change on the part of the bone marrow, and there is no sterobilin and urobilin. Moreover, in severe and chronic anemias there is no comparable generalized pigmentation, as one would expect were the theory of Von Recklinghausen correct.

On the other hand, hemorrhage and purpura have been features in a number of cases. Roth contends that there is an active blood destruction, though in his opinion this does not satisfactorily account for the whole picture. He cites cases with the blood picture and clinical findings of pernicious anemia. The fact that the majority of the cases show no blood change he explains on the ground that there is an active compensatory erythrocythemia. Roth claims to have seen in the spleen and lymph glands small, irregular forms of red blood cells as well as young and immature cells. Rössle[10] demonstrated the

6. Parker: Case of Bronze Diabetes, Brit. M. J., **2**:1052, 1903.

7. Von Recklinghausen: Ueber Hemochromatose, Tagebl. d. Versammel. d. Naturf. u. Aertzte, 324, 1889.

8. Opie: Hemochromatosis and Bronze Diabetes, J. Exper. Med., **4**: 279, 1899.

9. Anschütz: Diabetes with Bronze Skin; Hemochromatosis and Atrophic Pancreas, Deutsch. Arch. f. klin. Med., **62**:411, 1899. Blumer: Bronze Diabetes and Hemochromatosis, New York M. J., **94**:922, 1911. Muir: The Iron Content of the Organs in Bronzed Diabetes (Hemochromatosis), J. Path. & Bact., **19**:226, 1915. Ungebener: Ein Fall v. Bronzediabetes und besonderer Berücksichtigung des Pigments, Virchow's Arch. f. path. Anat., **216**:86, 1914. Cecil: A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, J. Exper. Med., **2**:266, 1909. McClure: Metabolism in a Case of Hemochromatosis, Arch. Int. Med., **22**:610 (Nov.) 1918

10. Rössle: Phagocytosis in Hemochromatosis, Beitr. z. Path. Anat. u. Allg. Path., **41**:181, 1907.

phagocytosis of the red cells by parenchymatous cells. He explained the disease on the basis of injury to capillary walls with numerous minute scattered hemorrhages.

There is still another possibility, however. It is the consensus of opinion that dead red blood cells are disposed of in a definite way, that is to say, they are destroyed by the spleen and their useful elements, particularly the iron, is stored or resynthetized by the liver. In this connection it is significant that the great mass of the iron accumulation in hemochromatosis occurs in the liver. From this point of view it has been easy for many authors to assign the burden of the responsibility to disturbances of the hepatic function. The presence of pigment elsewhere they assume to be the result of transportation of pigment from the liver, although the method of transportation has not been demonstrated. This does not explain the relatively great quantity of iron in the pancreas and the spleen.

For our own part, we are inclined to agree with Roth, Abbott and others, that there is some toxic agent at work which simultaneously produces injury to the erythrocytes and to the cells of the parenchymatous organs. There is then more circulating iron than in normal conditions, making for its greater accumulation in injured cells.

The Relation of Cirrhosis.—The sequence of events in the liver merits careful consideration, since it is the scene of most extraordinary changes, notably in the form of massive and diffuse accumulations of iron pigment and accompanying connective tissue overgrowth. There are three possible explanations of the changes occurring in the liver:

1. That pigment is deposited and that there is a reaction to a foreign body in the form of connective tissue proliferation.

2. That the cirrhosis has so injured the cells that they become a ready depository for excess mobile iron.

3. In common with other cells of the body the liver cells have sustained toxic injury. In reacting to this, connective tissue is laid down precisely in the same manner as we are accustomed to conceive in cirrhosis of the ordinary type. Synchronously with this, is the deposition of iron representing the unperformed work of the injured cells of the liver in the metabolism of iron.

A certain proportion of all uncomplicated cases of cirrhosis of the liver, if examined for iron-containing pigment, give Perl's reaction. We found four cases among the necropsy protocols of the 5,000 Bellevue Hospital records that were marked enough to suggest hemochromatosis, although the remaining organs were not pigmented. Abbott cites Kretz's twenty-six cases of cirrhosis of the liver with iron pigment present in fourteen of them. In our cases we have found fibrous changes associated with massive extracellular collections of pigment.

The relationship of hemochromatosis to diabetes mellitus constitutes a problem of interest and importance, particularly with reference to the changes in the pancreas. Thus, in the great majority of all cases of bronze diabetes which have appeared in the literature of medicine, pigmentary or other alterations in the islands of Langerhans were described as totally lacking. In diabetes mellitus, as ordinarily encountered, lesions in the pancreas occur in about 88 per cent. of cases, and consist of sclerotic or hyalin alterations in the islands of Langerhans, withdrawal of the secretion of these isolated groups of cells so interfering with carbohydrate metabolism as to permit the continuous excretion of glucose in the urine. In occasional cases, however, the only demonstrable change in the pancreas in diabetes mellitus consists of extensive connective tissue replacement, the islands remaining unaffected. In these circumstances the question arises as to whether the pancreas has anything at all to do with the production of the diabetic changes, or whether the diabetes is to be regarded as of extrapancreatic origin, the sclerotic changes in the pancreas constituting merely an incidental anatomic feature. This interpretation is of interest in connection with the experimental work of Scobolew, who demonstrated that ligation of the pancreatic duct was followed by atrophy and connective tissue replacement of the parenchyma, the islands of Langerhans remaining intact. If, however, the fibrous mass with its embedded islands is now removed, the animal promptly develops diabetes.

In hemochromatosis with diabetes, histologic changes in the islands of Langerhans, such as sclerosis or hyalin transformation, are practically unknown, and to implicate the pancreas as the cause of the diabetes necessitates assuming changes in the islands which are not demonstrable by ordinary histologic methods, since it is obvious that the mere presence of pigment in the interstitium, with or without connective tissue overgrowth, is insufficient to account for the metabolic disturbances in question. That insular changes of the sort indicated do exist has been shown by Symmers,[11] who, in the islands of Langerhans of alcoholic subjects, demonstrated the presence of extensive fatty changes, using, however, special stains to bring them out, such as sudan III. In ordinary hematoxylin and eosin preparations the islands appear to be normal. Symmers, correlating these histologic changes in the islands of Langerhans in alcoholic subjects with the known fact that alcohol habitués are intolerant of sugar and excrete it in the urine when fed it in slightly excessive quantities, accounts for the intolerance on the basis of definite anatomic changes in the islands of Langerhans.

11. Symmers: The Occurrence of Fat in the Islands of Langerhans, Arch. Int. Med., **3**:270 (Feb.) 1909.

All things being considered, however, we believe it highly probable that the diabetic changes which are associated with hemochromatosis are dependent on changes outside the pancreas.

Summary of Cases Reported in the Literature.—At the time of this writing, eighty-one cases of hemochromatosis have been reported. Of these the records of seventy-five were available for study.

Liver: Information regarding this organ was found in fifty-three cases. The liver was generally enlarged. Clinically, it was described as slightly enlarged in 60 per cent., moderately in 10 per cent., and markedly in 4 per cent. No enlargement was made out in 20 per cent. of the cases examined. At necropsy, however, 95 per cent. were recorded as enlarged. Twenty-six cases with exact weights showed an average of 2,400 gm. Cirrhosis occurred in 96 per cent. and iron pigment in all cases. The color of the liver varied from brownish red to chocolate. Ascites occurred in eighteen cases. In the majority of cases the mass of iron pigment was found extracellular in the connective tissue. This was usually an amorphous collection. It also occurred in great quantities in the liver cells, which then tended to show signs of degeneration in their poor staining qualities and rather irregular and pycnotic nuclei. Intracellular pigment was always present in fine brown granules. This pigment could often be demonstrated beautifully in Kupfer cells, endothelial cells of capillaries, bile duct cells, and connective tissue cells. Occasionally a finer and lighter brown pigment which failed to respond to Perl's test could be demonstrated in the vessel walls and the capsule. This corresponds to the so-called hemofuchsin.

Pancreas: Data concerning the pancreas were obtainable in sixty-five cases. Varying from golden brown to bronze in color, iron holding pigment was present in all cases. Of fifty-two cases with a record of the amount of connective tissue, forty-eight showed marked fibrosis. The islands of Langerhans were rarely affected. Eighty-five per cent. of the fifty-eight cases with records showed a moderate glycosuria (average of 5 per cent.).

Spleen: Clinical data concerning the size of the spleen were obtainable in forty-eight cases. In fifteen cases the spleen was referred to as slightly, twice as moderately, and twice as considerably, enlarged. In the remaining twenty-nine cases it was not felt.

At the time of the postmortem examination, from fifteen cases with available weights we find an average of 400 gm. Pigment on gross examination was only noted occasionally, but on microscopic study a small amount of pigment was usually to be seen. The spleen was usually firm, a few times it was soft.

Lymph Nodes: The most marked changes were seen in the abdominal nodes. The fact that such nodes are in the line of lymph

drainage from the liver and pancreas has been used as an argument in favor of the idea that there is an active transportation of pigment. Thirty-five of forty-four cases describe massive collections of iron pigment; in some cases this was very extensive, replacing the structure of the organ. There was usually marked evidence of fibrosis. Grossly, the glands were enlarged, shading from a brown to a chocolate color, and usually firm. There are instances, however, in which the glands were extremely soft, in some cases actually diffluent.

Skin: The microscopic studies of the skin are disappointing because there is a wide disparity between the striking clinical appearance and the postmortem findings. Iron pigment in the skin was usually scant and found only in the sweat glands. It occurred in about one-half of the cases.

Heart: In only twenty-two cases among the seventy-five available for study was the heart described. One-half of these showed hemosiderin within the muscle. This was situated intracellularly at the nuclear poles. In one case only did the connective tissue contain iron pigment. Fibrosis of the organ was reported once, and was not of marked degree.

Kidney: Of twenty-three cases described in the literature, sixteen showed iron pigment, always in small quantities, within the epithelial cells of the tubules. Only once (Strater's case [12]), was pigment described in the glomerular tuft. Five cases showed another light brown pigment which we believe was iron pigment not properly demonstrated by Perl's stain.

Gastro-intestinal Tract: Histologic data were available in nineteen cases. Six cases showed iron pigment in the small intestines situated intracellularly in the depths of the glands. Twelve cases showed an iron free pigment in the muscularis mucosa. The duodenum and the first part of the jejunum seemed to be the most favorable site for pigment deposit. The stomach seemed to be a less favorable site than the intestine.

Suprarenals: The condition of the suprarenals was mentioned in thirteen cases. Ten showed the presence of iron pigment consistently found in the cortex.

Lungs: The lung seems to be one of the organs which is relatively free of iron deposit. Eleven cases gave histologic data. In only two was iron pigment observed and then in very small amounts.

Thyroid: Nine cases of the eleven describing this gland showed the presence of moderate amounts of iron pigment. Here, as is usually

12. Strater: Beiträge z. Lehre v. der. Hemochromatose und ihren Beziehungen z. allegemeinen Hemosiderose, Virchow's Arch. f. path. Anat., **218**:1, 1914.

the case in organs rich in parenchyma, the deposit was in fine granules, situated intracellularly, within the epithelial cells lining the acini. The connective tissue was always reported free of iron pigment.

Prostate: The epithelium of the gland cells contained iron pigment in eight of nine cases reported. The connective tissue contained iron pigment in two cases, while in two others, an iron free pigment was described. Sprunt [4] reports a case in which the seminal vesicles and vas deferens were rich in iron pigments.

Testes: In eight cases only the testicles were studied for pigment. In two an iron containing pigment was found in the endothelium lining the small blood vessels and capillaries. In six cases an extracellular iron free pigment was seen in the seminal canals.

Parathyroids: In only two cases have we found the parathyroid described. Both of these contained iron pigment, moderately once, in the other case in huge amounts. The pigment was intracellular in both.

Bone Marrow: The bone marrow was examined in eight cases. It was usually hyperplastic, and in seven cases iron pigment was present both intracellularly and extracellularly. One case showed no pigment.

Brain: Cerebral hemorrhage was present in two of the seventy-five cases reviewed. Histologic examination in these cases revealed no iron pigment.

Hypophysis: Two cases have been studied as to the presence of pigment in the hypophysis. In both it was observed in the parenchymatous cells and in one in the connective tissue.

REPORT OF CASES

Case 1.—Male, aged 50 years, expressman. In the hospital three days. Duration of the disease twenty-one days.

Past History.—Never sick in his life. Denies venereal disease. Drinks from four to five beers a day and whiskey in small quantity.

Present Illness.—Three weeks ago injured right side in a fall from a wagon. Was unconscious at the time. From that time on was in the hospital complaining of pain in the right side and shoulder. He passed no blood in the urine or stools. His bowels were regular and his appetite fair.

Physical Examination.—His skin was dark brown in color and was thought to have a case of "vagabonds' disease." His heart was negative. There were signs of hypostatic congestion at the pulmonary bases which increased until the time of his death. The abdomen was enlarged with gas. The liver and spleen were not felt. He died after three days in the hospital.

Urine.—Sp. gr., 1.020; cloudy; acid; no albumin. Casts, red blood cells, leukocytes and sugar present.

Chemical Blood Examination.—Carbon dioxid tension normal. Sugar, 471 mg./100. Temperature: From 100 to 106 F.; pulse from 80 to 40; respiration, from 24 to 52.

Clinical Diagnosis.—Diabetes. Hemochromatosis. Perinephritic abscess.

Necropsy Report.—The body is that of an emaciated male. The conjunctivae are icteric. Skin of face, neck, forearms and hands bronzed. Fifty c.c.

of pericardial fluid. The right lower lobe is the scene of a bronchopneumonia. There are basal adhesions. The liver weighs 2,715 gm. It is brownish red in color and coarsely nodular. Lobules are indistinct. The pancreas is long and thin and brownish red in color. Spleen weighs 920 gm., is dark red in color and grumous. The suprarenals show an enlarged brownish red medulla. The right kidney is larger than the left. The testes are normal. The intestines are normal, except for the duodenum and jejunum. Here the mucous membrane is colored brown. There is fluid in the abdomen. Anatomic Diagnosis: Cirrhosis of liver and diabété bronzé; chronic splenomegaly; hemochromatosis; chronic hyperplastic gastritis; suppurative nephritis and perinephritis (right), and suppuratve prostatitis and periprostatitis; moderate pial edema; terminal sepsis.

Microscopic Examination.—Liver: There is a moderate degree of cirrhosis. Coarse strands of connective tissue interrupt somewhat the normal architecture of the organ, but there is not the advanced overgrowth noted in some cases. The formed connective tissue is fairly cellular and contains many capillaries and budding and regenerating bile ducts. The liver cells are fairly well preserved. Their nuclei are only slightly smaller than normal and a bit irregular.

Pigment is present in all of the liver cells, but the majority of it is found in massive collections in the connective tissue septums. In the liver cells, the pigment is more or less diffuse, occurring in the form of discrete brown granules, which are not numerous. However, Kupfer cells scattered among them are fairly bursting with quantities of the pigmented granules. Some of the connective tissue pigment can be made out as lying in the cells, some is apparently in the lymph channels; very little, if any, appears in the new formed bile ducts. The greater part of the pigment, as was said, is aggregated together into the extracellular amorphous collections. Practically all of the pigment gives the reaction for iron.

Heart: With Perl's method quantities of greenish blue pigment is brought out in the heart muscle cells. Much of it is an exaggeration of the bipolar arrangement. There is also some amorphous pigment outside of the cells. In the connective tissue and fat there is a small amount of hemofuchsin. The inner coats of the coronaries show the same pigment. There is a slight fibrosis of the myocardium.

Pancreas: There is a fair amount of perilobular fibrosis here. The pigment is chiefly aggregated in this position and is mostly extracellular. There is also pigment in the cells of the acini and in the cells lining the ducts. The islands of Langerhans are very few in number and small. With Perl's test most of the pigment stains dark green. That in the gland cells tends to retain its yellow brown color.

Kidney: Cloudy swelling; multiple small abscesses. In a very few of the cells of the convoluted tubules scattered blue reacting granules can be seen.

Spleen: A small amount of pigment diffusely scattered can be observed. It reacts positively for iron, and lies in the mononuclear cells for the most part. The connective tissue fibers of the capsule are encrusted with iron salts.

Suprarenals: The glomerular zone shows a massive intracellular collection of iron reacting pigment. There is only the slightest amount of pigment in the reticular zone. The pigmentation is entirely confined to the cells.

Skin: There is a small amount of yellow pigment in the cells of the papillary layer and also in the connective tissue of the walls of the veins. No reaction for iron is obtainable.

Intestines: A beautiful contrast is seen in this section between the blue iron containing pigment in the basal cells of the ducts and the fine yellow granules in the muscularis mucosa, which do not give the iron reaction.

Prostate: Normal.

Testes: Show no pigment and are apparently normal.

Case 2.—Male, aged 49 years, clerk; in the hospital seven days. Duration of the disease six months.

Past History.—Diseases of childhood. No illness for ten years. Has dizzy spells. Venereal disease denied. Drinks a little beer but no whiskey.

Present Illness.—For six months he has had thirst and polyuris. During this time his private physician has found sugar in his urine. He dieted and lost thirty-five pounds. A roentgen-ray examination of the liver six months ago was said to show carcinoma of that organ. For two months his abdomen has been getting larger.

Physical Examination.—The face is a dusky hue. Collateral circulation established over the body. Heart is negative. Lungs show congestion at the bases. The abdomen is large and contains fluid. The liver can be felt 21 cm. below the costal margin. It has a roughened border. There are no enlarged lymph nodes. He grew gradually worse, complaining very little and died seven days later.

Urine: Sp. gr., 1.035; cloudy; acid; no albumin present; no casts. Leukocytes and sugar present.

Wasserman: Negative.

Chemical Blood Examination.—Carbon dioxid, 86. Sugar, 300 mg. per 100 c.c.

Clinical Diagnosis.—Diabetes; carcinoma of the liver.

Temperature: From 97 to 98 F.; pulse, from 78 to 120; respiration, from 20 to 26. Blood pressure, 130/85.

Necropsy Report.—The body is that of an emaciated male adult. The face and neck are bluish. Heart muscle is brownish in color, flabby and the wall is thin. The lungs show small tumor nodules on the pleural surface. The liver is very large, weighing 5,085 gm. It is brownish red in color and finely granular. On section it shows multiple tumor nodules throughout. The bile is tarry green in color. The pancreas is larger than normal and there are tumor nodules throughout it. It is reddish brown in color, and the connective tissue appears to be increased. The spleen is normal in size and brownish in color. The connective tissue is apparently not increased. The follicles cannot be seen. The lymph nodes at the hilum of the liver as well as those lying retroperitoneally present a peculiar appearance. They are reddish brown in color and almost diffluent. The kidneys are normal, except for a slight brownish color. The suprarenals show a dark brown cortex. The esophagus, stomach and large intestine are normal. From the pylorus to the iliocecal valve the mucous membrane of the intestine is greenish black in color. The thymus is small and bluish red in color. The brain is normal.

Anatomic Diagnosis: Brown atrophy of heart; multiple pleural metastases in lung; primary carcinoma of the liver; hemochromatosis of spleen, suprarenals, kidney, pancreas, retroperitoneal nodes, duodenum, jejunum, ileum, liver; secondary carcinoma of peritoneum with ascites; few metastases in pancreas; multiple pigmented atrophic tibial scars.

Microscopic Examination.—Liver: The liver is the site of a primary carcinoma. There is in addition a marked cirrhosis. Iron staining pigment is seen in considerable amounts in most of the remaining parenchymatous cells, also in many of the cells of the new growth. There is a moderate amount of iron staining pigment in the connective tissue both intracellular and extracellular and a small amount of fine yellow pigment in the connective tissue which does not give the iron reaction. The duct cells and endothelium of the blood vessels and sinuses contain practically no pigment.

Pancreas: There is a considerable increase in the amount of interlobular connective tissue. The islands of Langerhans are normal in number and size but some of the cells contain iron pigment. The blue staining iron pigment is seen chiefly in the cells of the acini and the duct cells in fine granules.

In the connective tissue both intracellularly and extracellularly there are amorphous deposits of various sizes appearing as a green pigment with the hematoxylin and eosin stain, and of a faint yellowish-brown tinge with the iron stain.

Lymph gland: Huge masses of green pigment taking the iron stain almost entirely replace the pulp. Few lymphocytes remain. The connective tissue septums show only a slight yellowish shimmer with the hematoxylin and eosin stain. With the iron stain all of the connective tissue septums are colored a beautiful Prussian blue, suggesting a diffuse incrustation of iron. The vessel walls are literally pipes of iron.

Skin: The hematoxylin and eosin section demonstrates a moderate amount of fine, light brown granular pigment in the cells of the sweat glands. With the iron stain there are a few fine blue intracellular granules and a moderate connective tissue incrustation. There is no pigment in the epidermis or other structures.

Testes: In a few localized areas there is a blue staining iron pigment in fine granules. This is extracellular and is situated chiefly in the tunica vaginalis and the connective tissue between the seminiferous tubules. Between the seminiferous tubules there are many large mononuclear leukocytes which contain a considerable quantity of light yellow pigment, sometimes in granules, sometimes diffusely distributed. This does not take the iron stain. Elsewhere the section is normal.

Epiglottis: The section is normal, except for quantities of fine granular pigment lying in the cells. There is also a small amount of granular blue pigment in some of the cartilage cells.

Large Intestine: A slight scattering of blue granular pigment on the surface of the glands of the mucous membrane is undoubtedly an artefact. There is a slight yellow pigmentation in a few of the muscle cells. Otherwise the sections are normal.

Prostate: The cells of the acini contain a moderate amount of granular iron pigment. In marked contrast to this are yellow granules of pigment seen within the spindle cells of the interstitial tissue which do not stain with Perl's method.

Thyroid: The acini contain a small amount of colloid and are about normal in size and number. The epithelial cells are loaded with huge amounts of blue staining pigment. In some places iron pigment is seen extracellularly in the connective tissue. There is no other kind of pigment present.

Lungs: The lungs contain many erythrocytes and phagocyting epithelial cells laden with broken down erythrocytes. However, with the iron stain there is no evidence of the presence of hemosiderin. The disintegrated erythrocytes appear as a granular dark brown amorphous material.

Choroid Plexus: Most of the cells contain a large amount of finely granular blue staining iron pigment. This is quite uniform.

Suprarenals: The suprarenals contain no iron pigment. The glomerular zone contains a moderate amount of intracellular, coarse brown amorphous pigment which does not take the iron stain.

Kidney: The kidney section shows the epithelium of the tubules and the glomeruli very much swollen. There is no pigment present with any of the methods of staining used.

Optic Nerve and Retina: There is brown pigment in the basal cells of the retina, probably melanin. With the iron stain there is no blue pigment except for a slight incrustation of the connective tissue.

Case 3.—Male, aged 56 years; in the hospital one month; doesn't know how long he has been ill.

Past History.—Venereal disease denied. Drinks only a little beer. Pneumonia three years ago.

Present Illness.—Patient is stupid and complains of pain in the knees and difficulty in walking. He sleeps well, has no headache, and his appetite is good.

Physical Examination.—His skin is a dusky bronze color. Heart and lungs are negative. The abdomen is normal and neither the liver nor the spleen can be felt. The left knee joint is tender. While in the hospital his nose

bled for twenty-four hours continuously. He reports that six months and one month ago, respectively, the same thing happened. While in the hospital, the pigmentation gradually increased and involved the mucous membrane of the mouth. He became dyspneic and drowsy before death.

Urine: Sp. gr., 1.015; clear; acid; no albumin or casts; sugar negative. Was given 30 gm. of glucose without producing glycosuria.

Blood: Erythrocytes, 3,800,000; Hb., 70 per cent.; leukocytes, 10,200; polymorphonuclears, 68 per cent.; slight anisocytosis and poikilocytosis.

Blood Sugar: From 214 to 421 mg. per 100 c.c.

Temperature: From 97 to 99 F.; pulse, from 60 to 90; respiration, from 18 to 24. Blood Pressure: 165/80.

Clinical Diagnosis.—Addison's disease.

Necropsy Report.—The body is that of an adult male of large frame. The sclerae are icteric. The gums are bluish in color. The skin is somewhat dark in color and there are a few brown spots on the abdomen. The heart is brownish yellow in color and shows on section a moderate amount of scarring. The pericardium contains a moderate amount of hemorrhagic fluid. The lungs are normal. The liver weighs 2,100 gm. It is brownish red in color. The surface is smooth with slight lobulations. The pancreas is large and brick red in color. The lobulations are normal in configuration. The spleen weighs 255 gm. It is brick red in color and grumous. The bronchial and abdominal lymph nodes are enlarged, brownish in color, and very soft. The kidneys are asymmetrical. They are otherwise normal. The suprarenals are normal. The testes are normal. The glans penis is greenish yellow in color. The esophagus and small intestine are normal. The stomach and colon are dark green on the inner surface. The cartilages of the ribs are green on section. The bone marrow is red and active looking. The synovial membranes of the knee joints are yellowish brown in color.

Anatomical Diagnosis: Hemochromatosis; emphysema and acute and chronic bronchitis; acute pulmonary congestion and edema; hemopericardium; slight chronic interstitial myocarditis; slight chronic aortitis; chronic perisplenitis, splenic tumor with pigmentation; small right kidney (arterio sclerotic); large left kidney; moderate acute parenchymatous hepatitis; large pigmented pancreas; pseudomelanosis of large intestine; carious teeth, pyorrhea and gingivitis; pigmented synovial membrane in knee with arthritis.

Microscopic Examination.—Liver: Bands of connective tissue interlace to form coarse lobulations. The scarring, however, is not extremely marked. The liver cells, on the other hand, stain poorly. They are small and show somewhat pyknotic nuclei. They uniformly contain quantities of dark brown granules. In this case, as in the previous one, the greatest deposits are in the connective tissue. Here it appears as masses of various size lying outside of the cells. The connective tissue cells contain very little. The duct cells are noticeably free. The distribution of the pigment is such that the greatest quantity lies at the periphery of the lobules. Studied for iron the reaction is a dark bluish green color, which is undoubtedly positive. In the walls of the vessels a few fine yellow granules which do not react for iron can be seen.

Pancreas: There is a moderate interlobular and interacinar fibrosis. The acini as well as the islands of Langerhans appear normal. Almost all of the pigment is interacinar, the connective tissue being relatively free. The pigment everywhere appears as pure blue granules, with the iron stain. The cells of the acini, islands and duct cells, contain the largest amount of pigment.

Lymph Nodes: The lymph nodes are almost entirely replaced by brown pigmented cells. Thick trabeculae of connective tissue can be seen everywhere. The germinal centers in the small nodes contain the pigment, while at the periphery of the lobule, the normal lymphoid arrangement is present. In the nodes with little pigment, the endothelial cells of the sinuses seem to be involved chiefly, but in the large nodes with extensive change, all the cells

become pigmented. The connective tissue stains a pale lavender with the hematoxylin and eosin stain and with the iron stain all the pigment presents a blue color.

Heart: The muscle is markedly thickened.

Spleen: The splenic architecture is maintained with little increase of connective tissue. Arranged fairly regularly about the trabeculae are numerous large mononuclear cells full of brown granular pigment. These large cells are seen also within the pulp, some clumped and some in strands. With the iron stain blue granular pigment is seen in all of the cells of the pulp and in the large mononuclear cells just described. The fibrous elements show a moderate incrustation.

Stomach: The structure is normal, save for a small amount of finely granular blue pigment, situated intracellularly in the epithelium at the base of the glands. It is fairly well distributed in this location throughout the section.

Lungs: The section shows a marked congestion and a slight scarring of the tissue. The interalveolar tissue contains large mononuclear and polymorphonuclear cells which contain anthracotic pigment. There are also numerous large mononuclear cells which contain fine blue granules when stained by Perl's method.

Kidneys: A marked glomerulotubular nephritis is present. No pigment can be seen.

Suprarenals: There is present a fine granular pigment situated intracellularly in the glomerular zone of the cortex. This takes the iron stain. There is no evidence of fibrosis and no pigment is present elsewhere.

Prostate: All the structure of the prostate appears normal. In the blood vessel walls there is a finely granular iron staining pigment situated intracellularly in the connective tissue. No pigment is seen elsewhere.

Bone Marrow: The bone marrow is hyperplastic. Many of the large myelocytes are seen to contain a moderate amount of iron pigment in fine granules. There is none seen elsewhere.

Testes: Structure is normal. No pigment is present.

Aorta: No pigment is present.

CASE 4.—Male, aged 56 years; in the hospital two months. The whole duration of the present illness is eighty days.

Past History.—Typhoid fever, fifteen years ago. Neisser infection, several times. Denies syphilis. Drinks seven or eight beers a day and whiskey occasionally.

Present Illness.—Has had no appetite for two weeks. Legs have been weak and he has had pain in the back.

Physical Examination.—The skin is icteric. There is cyanosis of the face, edema of the conjunctivae, legs and back. The heart shows mitral insufficiency and dilatation. Fluid in both chests. The abdomen is enlarged and contains fluid. The liver and spleen are not felt. The right knee, spine and pelvis are tender, and have been so for two weeks. Both chest and abdomen were tapped successfully.

Urine: Sp. gr., 1.025; clear; acid; albumin, sugar and bile negative. Erythrocytes present.

Blood: Erythrocytes, 3,000,000; Hb., 75 per cent.; leukocytes, 9,000. Spectroscopic examination of the blood normal.

Temperature, from 98 to 101 F.; pulse, 72; blood pressure, 105.

Clinical Diagnosis.—None.

Necropsy Report.—Emaciated male adult. Skin and conjunctivae icteric. Face and neck brownish. Heart muscle is brown and pale. There is a lobular pneumonia at the right base. There are also basal adhesions. The liver is small. It is greenish brown in color. It is finely and coarsely granular. The pancreas is large and flabby. It is coffee colored. The peripancreatic and

retroperitoneal nodes are anthracotic and cheesy. Kidneys, adrenals, testes normal. Thyroid shows no alteration. Bile stained clear fluid in the abdomen. Elevated yellow foci over the entire peritoneum.

Anatomic Diagnosis: Atrophic cirrhosis of the liver; ascites, icterus, chronic granular peritonitis; chronic hyperplastic perisplenitis; brownish pigmentation of pancreas and retroperitoneal lymph nodes; chronic adhesive pleurisy, emphysema and chronic bronchitis; tuberculous lymphadenitis of peripancreatic and retroperitoneal lymph nodes; lobular pneumonia; multiple erosions of gastric mucosa; scoliosis, osteoporosis general and fragilitas ossium; esophageal varices with melena.

Microscopic Examination.—Liver: There is a moderate grade of cirrhosis. The capillaries throughout the liver are tremendously dilated. The liver cells are swollen and stain badly and there is a rather widespread round cell infiltration which is particularly marked under the capsule. With hot hydrochloric acid and potassium ferrocyanid most of the pigment gives the iron reaction. This case is remarkable on account of the fact that practically all of the pigment occurs intracellularly. It is found in both liver and connective tissue cells. Striking also is the amount of pigment that is to be found in the endothelial cells of the capillaries and also in the lining cells of the bile ducts. The findings in the liver in this case suggest a rather more acute termination than occurred in the others.

Thyroid: The acini are filled with colloid. The gland cells are crowded with iron holding pigment. There is no evidence of injury to the parenchymatous cells. The connective tissue is normal in amount and is the scene of no pigment deposit.

Lymph Nodes: The mesenteric nodes show the presence of a chronic tuberculosis. There are quantities of brown pigment, chiefly extracellular. Some pigment, however, is to be seen in the large mononuclear cells. Studied by Perl's method, most of the pigment gives the dark green color, and lies in coarse amorphous clumps. That which is still granular and within the cells stains blue.

Spleen: There is a marked thickening of the capsular connective tissue. Most of the pigment is found in this location by preference assuming a position near the side of the gland pulp. It also is to be found in the trabeculae. There is relatively a small quantity in the pulp cells. All of this pigment is hemosiderin.

Intestines: Nothing of note is to be observed, except the very small amount of pigment that occurs in the basal cells of the glands and in the muscularis mucosa. None of this reacts positively for iron.

Testes: In the connective tissue and in the endothelial cells there is pigment. In the supporting cells between the seminiferous tubules there is a small amount of fine yellow pigment. No iron reaction is obtainable.

Kidney: There is a mild chronic nephritis. The cells of the convoluted tubules are the site of an inconspicuous pigment collection. Perl's test fails to show the presence of iron.

ONE THOUSAND ONE HUNDRED FORTY-SIX GOITERS IN ONE THOUSAND SEVEN HUNDRED EIGHTY-THREE PERSONS

SIMON LEVIN, M.D.
LAKE LINDEN, MICH.

INTRODUCTION

Obscurity and darkness in the field of medicine excite the profession to research. This applies directly to the goiter question, where much has yet to be learned in order to unearth a causative factor which may act directly or indirectly, but, where possible, a careful study of a large series of persons will add, at least, a stepping stone to the necessary knowledge. In this country, before the last draft of men for our army, no thorough tabulation of thyroid enlargements in relation to large numbers examined, and to so many sections of the United States, could have been accomplished with any degree of accuracy. Previously, these data were collected from irrelevant groups, except in a few instances (O. P. Kimball and D. Marine [1]), but we must centralize our information about a thorough classification of many individuals in definite districts, and eventually, compare cause or causes from different areas. Bircher [2] and others in central and southern European countries have given us their results from such collections.[3]

Therefore, the opportunity appealed to me in the comparative tabulation in the draft which I reported in March, 1919.[4] Since that time, on account of the great many statements made and which are not based on any records as to the relative proportion of goiters at the various ages, in the sexes, in periods of life, etc., I examined 1,783 unselected persons, in 1918 and 1919 living in our community, which lies distinctly in the Great Lakes goiter belt, in their relations to enlargements of the thyroid.

I have chosen the district in Torch Lake and Schoolcraft Townships of Houghton County, Michigan. Here there happen to be three distinct water supplies; first, spring water from the Gregory Springs;

1. Kimball, O. P., and Marine, D.: Prevention of Simple Goiter, Arch. Int. Med. **22**:41 (July) 1918.
2. Bircher: Etiology of Goiter, Práctical Med. Ser., Surgery **2**:275, 1918.
3. Goyanes: Endemic Goiter and Cretinism in Spain, Endocrinology **4**:491 (July-Sept.) 1920.
4. Levin, Simon: Discussion of Goiter in Five Hundred and Eighty-Three Registrants, J. Mich. M. S. **18**:98 (March) 1919.

TABLE 1.—The Record of Examination of 1,783 Persons for Goiter in Torch Lake and Schoolcraft Townships, Houghton County, Mich., in 1918-1919

Age	Males	Females	Single	Married	Born Here	Born Elsewhere	Total Goiters
1	19	33	52	..	50	2	8
2	23	22	45	..	44	1	12
3	19	25	44	..	40	4	17
4	16	12	28	..	23	5	13
5	26	16	42	..	36	6	19
6	15	17	32	..	30	2	23
7	14	15	29	..	26	3	18
8	21	38	59	..	52	7	42
9	18	24	42	..	33	9	33
10	20	30	50	..	45	5	44
11	18	18	36	..	29	7	29
12	20	37	57	..	52	5	51
13	15	26	41	..	33	8	37
14	24	27	51	..	46	5	43
15	14	21	35	..	30	5	26
16	14	34	48	..	43	5	41
17	24	22	46	..	41	5	39
18	22	24	43	3	42	4	43
19	11	28	37	2	36	3	37
20	16	19	29	6	29	6	28
21	16	12	24	4	25	3	24
22	6	18	19	5	23	1	19
23	10	25	19	16	28	7	28
24	16	22	22	16	32	7	27
25	13	11	7	17	17	7	15
26	13	17	17	13	25	5	23
27	13	14	8	19	17	10	17
28	11	13	8	16	20	4	17
29	10	9	2	17	15	4	12
30	12	21	6	27	21	12	23
31	10	15	7	18	16	9	18
32	12	11	6	17	14	9	14
33	4	14	3	15	9	9	12
34	11	22	1	32	20	13	22
35	7	12	3	16	15	4	12
36	17	12	3	26	21	8	18
37	5	15	0	20	12	8	16
38	10	15	1	24	14	11	15
39	7	14	1	20	11	10	13
40	13	19	3	29	22	10	17
41	11	6	2	15	9	8	10
42	10	14	2	22	8	16	16
43	10	8	2	16	10	8	13
44	15	13	3	25	18	10	14
45	13	12	3	22	15	10	16
46	4	8	0	12	4	8	11
47	7	8	2	13	4	11	9
48	10	12	1	21	3	19	11
49	12	9	1	20	5	16	9
50	4	8	0	12	2	10	6
51	5	6	0	11	0	11	8
52	3	7	0	10	2	8	5
53	5	6	0	10	4	7	6
54	4	2	2	4	0	6	3
55	2	5	0	7	0	7	3
56	7	6	0	13	1	12	6
57	7	2	1	8	0	9	4
58	5	7	0	12	2	10	6
59	1	1	0	2	2	0	2
60	10	6	1	15	0	14	5
61	44	33	2+	66+	2+	31+	19

second, Lake Superior water, and third, well water, which is spring water. The people are Americans, the larger percentage of French Canadian extraction, above the average in intelligence and in living conditions. The unhygienic conditions usually found in the poorer districts are absent. Each home has plenty of sunlight and ventilation and a lot or two for gardening. I am personally and professionally acquainted with nearly every person examined. Therefore, my knowledge of them would be of greater value than a simple school examination of many strange groups, whether adults or children. I have compiled the results as shown in the charts, making them as complete and self explanatory as possible. The charts demonstrate very clearly the numbers and percentages in the various ages and sexes from new-born to 61 years plus, in their social and residential relationship, and various types of goiter found in these individuals. There were 790 males and 993 females; 242 full family records; 714 married and 1,029 single; 1,243 were born here and 538 were born elsewhere. Three hundred and forty-one of the latter lived here fifteen years or more.

The definitions used in these examinations were those usually in use.

Group 1.—Simple goiter is one giving no symptoms, except an homogeneous enlargement of both lobes and isthmus that may be small, moderate or large. Six hundred and eighty-two goiters were found to be in this group.

Group 2.—Adenoma, whether fetal or adult, is an enlarged thyroid with a circumscribed mass, or masses, occupying any portion or portions of the gland, being single or multiple. These tumors were classified as small, moderate and large. The cystomas could not always be differentiated macroscopically from adenomas, as our living surgical pathologic specimens demonstrate. Therefore, I classified that group as adenomas and cystomas. Four hundred and twenty goiters belong to this group.

Group 3.—Colloid goiter is an enlarged thyroid gland, firm, symptomless, except from pressure, all the gland involved. The gland feels firmer, doughier and of a different consistency than simple, having no circumscribed masses. Forty-four goiters belonged to this group.

Exophthalmic goiter was also noted, but the proportion was comparatively small. It is rather surprising that among so many goiterous individuals we see so few cases of true exophthalmic goiter, whereas, it is very common to see hyperthyroidism, especially during puberty and the menopause. I find that adenomas becoming active make up the larger proportion of the latter class. In my operative work, the partial thyroidectomies for hyperplastic adenoma for hyperthyroidism

also comprised a large proportion, which only signified that the danger from this phase predominates in the goiter situation in our section, pressure and cosmetic phases comprising a lesser proportion.

The record of infection in each individual was not complete, although many observations would justify my saying something further in this regard. Cretins are very rare in our community, and cases of hypothyroidism are not common. The two cretins here are members of goitrous families in which the maternal parent had a goiter. The families with definite morons are not common, but during the draft examination I found a few families with several morons in each family whose maternal parent or both parents had developed enlargements of the thyroid. I must grant that the numbers and percentages of goiters startle one on examination of the charts, but my observations can be verified by any capable observer who attends an evening or afternoon entertainment in summer.

TABLE 2.—Total Number of Persons and Different Types of Goiters

	Total Persons	Total Goiters	Group 1 Simple Goiters	Group 2 Adenomas and Cystomas	Group 3 Colloid Goiters
Males	790	355	230	119	6
Females	993	791	452	301	38
Totals	1,783	1,146	682	420	44

TABLE 3.—Percentage of Different Types of Goiters to the Total Number of Persons and Sexes Examined

	Total Persons	Total Goiters, per Cent.	Group 1, per Cent.	Group 2, per Cent.	Group 3, per Cent.
Males	790	44.9	29.1	15.0	0.76
Females	993	79.6	45.5	30.3	3.8
Totals	1,783	64.2	38.2	23.5	2.5

INFLUENCE OF WATER SUPPLY

The examination disclosed that the numbers and proportions of different types of goiter at the various ages and sexes did not vary with the different water supplies, in spite of the fact that the water from Lake Superior must be considerably diluted, and, therefore, any chemical or active virus must be in proportionate dilution. The spring water comes from bubbling springs from five to eight miles in a crow's path due east from the shore of Lake Superior. The former flows into a lake tributary (Torch Lake) of the latter twenty miles from the intake of the Lake Superior water supply station. An adequate idea of the location and relative distances can easily be acquired by a reference to a map of the Keweenaw Peninsula of Upper Michigan. Space does not permit me at this time to mention the

results of examinations of the various water supplies, but I may add that the waters about the county, whether spring water or Lake Superior water, from various sources, have a constant factor. The relation of calcium to sodium elements is always more than 1 : 1, and this relationship occurs but rarely in any other water supplies in the United States. The water supply has been given the credit for carrying the positive factor of goiter but in this incident, it does not assist us any in determining it. At some future date this study will continue and further information will be presented on this phase of the subject.

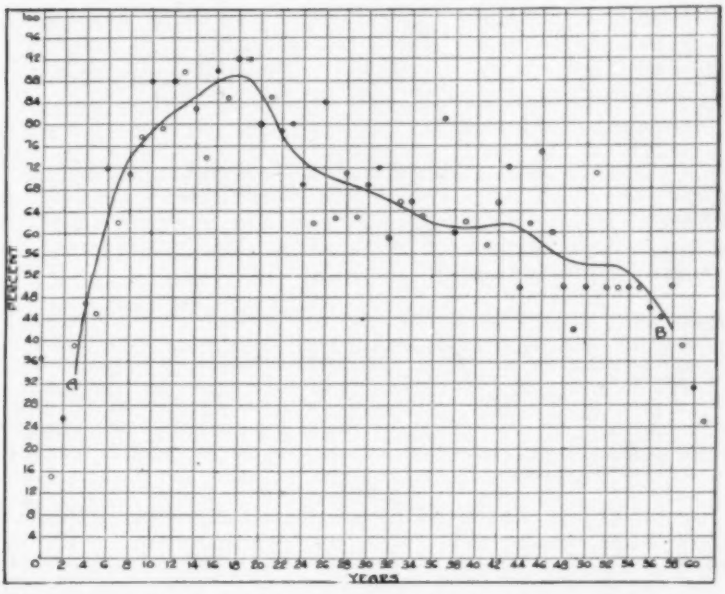

Chart 1.—Outline dots indicate percentage of total goiters to number of persons in each year in the 1,783 examined. AB, mean curve of percentages.

INFLUENCE OF AGE AND SEX ON INCIDENCE OF GOITER

The occurrence of goiter in age is so differently influenced by the nature of the sex, that a comparative study of these two factors would be more advantageous. The goiters commence at the first year in about 22 to 26 per cent. of those examined at that age, both sex percentages advancing rapidly towards puberty, much steadier in the female, whose percentage of total goiters in the period from 10 to 15 years being about 94, while that of the male averages about 68.

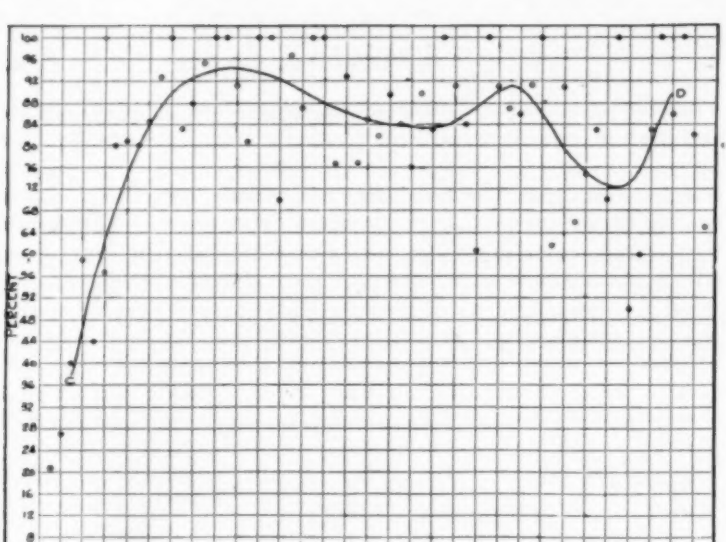

Chart 2.—Outline dots indicate percentage of total goiters to numbers in each year in the 993 females. CD, mean curve of percentages in five year averages.

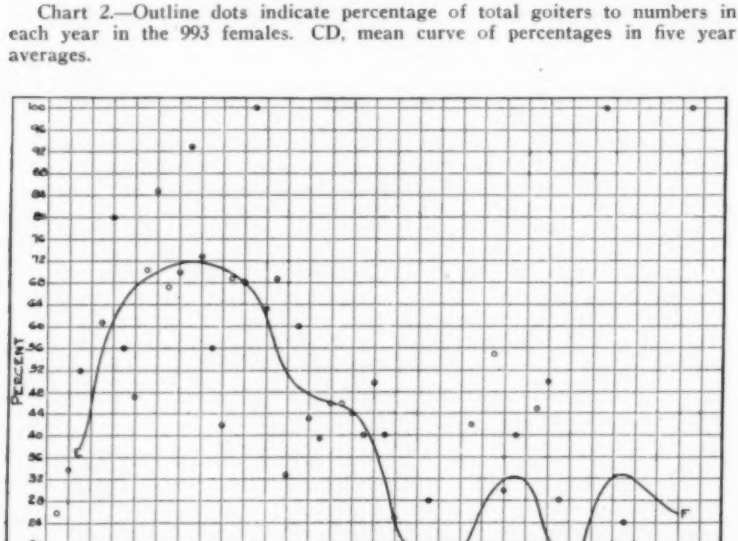

Chart 3.—Outline dots indicate percentage of total goiters to numbers in each year in the 790 males. EF, mean curve of percentages in the five year averages.

The mean curve of the goiter percentages in the female is maintained throughout life above 80 per cent., while that of the male drops very markedly to about 20 per cent. between 35 and 40 years of age, when it gradually rises to the height of 32 per cent. at 42, slipping down later with accidental fluctuations till 20 per cent. is reached near the end of life.

One can readily see that as the functions of the glands of internal secretions are more drawn on by the female at puberty, during child bearing and at the menopause, she has more reason for alteration and growth of this important gland. Therefore, the findings in the percentages demonstrate this fact very clearly. Her incidence of thyroid enlargement is maintained more steadily, not dropping as in the male, after the rise at puberty has been established. In the examination of women at confinement, more than 90 per cent. had their thyroids enlarged from just a palpable mass to a size that interfered with respiration, extending from chin to sternum and latterly bulging the sternomastoid as much as the muscles would permit. Adenomatous masses, simple goiter and normal gland tissue, under ordinary conditions of life, all became hypertrophies during pregnancy. The constant stimulating influence, coupled with the goiter belt irritation, no doubt helps to cause a permanent enlargement of the thyroid gland in these simple and adenomatous goiters.

DIFFERENT TYPES OF GOITER

An interesting fact that the tabulation and deduction of percentages of the two important groups of goiters by sex and ages has established, is that in the first half of life in both sexes, till 35 years of age, the maintenance of the large percentages of goiters is due to the simple enlargement of the gland, and that as the age arrives when growths are more prevalent, we see the adenomas and cystadenomas arriving to absolutely maintain the percentage in the female and the male. The curves show that puberty affects the growth to simple goiter earlier than the enlargement of the adenomatous masses. Therefore, the solid line declines at 16 years and the broken line declines at 19 years. Charts 4 and 5 plainly give this wonderful and startlingly clear information. The similarity in time of the appearance of growths corresponds very closely to our idea of growths in other vital parts of the human body, i. e., the cancer period commences at about 35 years of age, and fibromas of the uterus are more marked after from 32 to 35 years of age, etc. No absolute age of commencement of the growths can be established because, no doubt, there were embryonic retention nests potentially amenable to excitation of growth, growing slowly, from the very beginning.

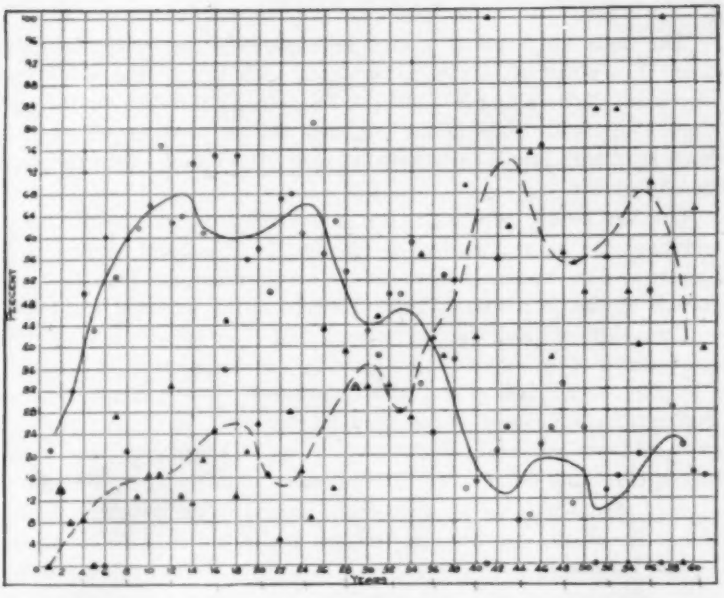

Chart 4.—Different types of goiters in 993 females from 1 to 61 years of age inclusive. Outline dots indicate percentage of simple goiters (Group 1) and solid triangles percentage of adenomata and cystomata (Group 2) to the total females examined for each year. Solid line, mean curve for Group 1; broken line, mean curve for Group 2.

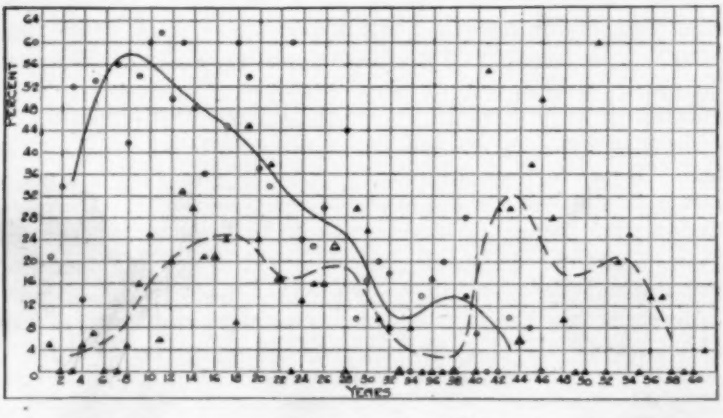

Chart 5.—Different types of goiters in 790 males from 1 to 61 years of age, inclusive. Outline dots indicate percentage of simple goiters (Group 1) and solid triangles percentage of adenomata and cystomata (Group 2) to the total males examined for each year. Solid line, mean curve for Group 1; broken line, mean curve for Group 2.

PARENTAL RELATIONSHIP OF GOITER

Out of the total numbers examined, mothers alone had goiters in 802 instances, fathers alone in twelve, and both parents 183 times. These figures are only complete as far as they go, because in some families neither the history nor observation could establish data sufficient to note whether the parent or parents had any enlargement of the thyroid.

In the families with four or more children, the family record being complete, it was found that the presence of goiter in both parents resulted in many goiters among the children. Adenomas in both parents, especially the father, meant adenoma in the children. According to Chart 6, which contains records of full families, the influence of the presence of goiter in the mother is four times as great as that in the father. The presence of goiter in both parents leaves the offspring without the smallest possible chance of not developing goiter, if they continue to live in this district.

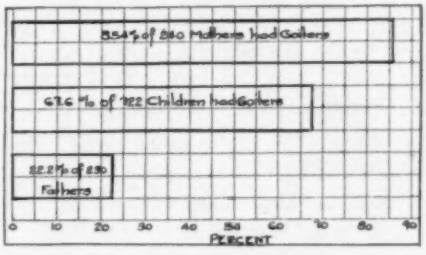

Chart 6.—Percentage of total goiters in 242 complete families with 1,192 persons.

REPORT OF CASES

1. Family A. P. Father and mother were born in Lower Canada and have adenoma in the right lobes of the thyroid. All the children, four girls and two boys, were born here, living here always. The eldest, a girl, aged 18, has a small simple goiter, but all the other children have adenomas in the right lobes, varying in size from small to large.

2. Family P. M. Father and mother born in Canada and had nine children, eight boys and one girl, all born here, living here always. The father has a small right adenoma, the mother has large multiple adenomas, and the four older children all have from small to moderate sized adenomas, the five smaller ones having small simple goiters.

3. Family L. P. Mother and father born in Canada and had eleven children, six boys and five girls, all born here, living here always. Parents both have adenomas of the thyroid and all the children, except a boy, aged 6, who has an adenoma, have from small to moderate sized goiters.

4. Family E. C. Father and all the children born and always lived here. The mother was born in Arkansas. Mother and father have large and multiple adenomas, respectively, and the children, seven boys and five girls, all except a 2 year old girl, have goiters (three have adenomas, and the others simple goiters).

There is, no doubt, an influence in the mothers with large exuberant thyroids to give birth to infants with enlarged thyroids. Some of the latter are large enough to cause distinct pressure.

In my experience of nearly twenty years in this section, I have never seen a nongoiterous mother bear a goiterous child, but many women with goiters, whose thyroid and goiter enlarged immensely during pregnancy, bore children with distinct enlargements of the thyroid, and, furthermore, nearly all of her children were born with the same enlargement of the thyroid. We can, with reason, draw the conclusions that influences that mean enlarging active thyroids in the mother are carried through the placenta, causing a corresponding enlargement of the fetal thyroid, and also, that no doubt it is of a chemical nature acting positively or negatively. An interesting point is that these large fetal thyroids disappear in from seven to fourteen days after birth, even though the child is nursed by its mother. Therefore, this transmitted influence passes through the placenta and not in the mammary secretion, the child acquiring it later in life. Some of these children at birth have the appearance of cretins with short noses, short stubby hands and the expression of idiots.

INFLUENCE AND LIABILITY OF DEVELOPMENT OF GOITER

In reviewing histories of the numbers who suffer from certain types of enlarged thyroids, simple, adenomatous, cystic and colloid goiters, we must conclude that enlargement of the thyroid maintained by living continuously in thyroid belts will be permanent. These glands can only be treated by surgical intervention. This applies more directly to adenomas that have the potentiality of varying in size and becoming plain tumor masses and thyrotoxic.

One thousand two hundred and twenty-three persons were born here and 538 were born elsewhere. Of the latter, 341 lived here fifteen years, 54 lived here from ten to fourteen years, 68 lived here from five to nine years, and 75 from one to four years, inclusive. This makes more than 80 per cent. of the total number subjected to the same local influence by birth or by residence for fifteen years or more. Therefore, if one were born elsewhere in a non-goiterous region and moved to this district, the liability of becoming goiterous would depend on the length of residence and the age of attaining the same. Therefore, we may deduce from these figures and other observations that, being born or acquiring a residence of fifteen years or more here, would entitle one to an enlarged thyroid according to the percentages for that year (Charts 1, 2 and 3). The danger, if the individual continued his residence, increases inversely with the age of attaining the latter.

The liability of goiters developing in persons born here is as follows: Females, aged 13 years and over, 80 per cent.; males, between 13 and 35 years, 66 per cent., and males between 35 and above, 45 per cent. (Charts 2 and 3).

The liability in Group 2 is as follows: Females from 5 to 35 years, 20 per cent.; females, 35 years and above, 62 per cent.; and males from 5 years and above, 20 per cent. (Charts 4 and 5).

RELATION OF INFECTION

In analyzing those who have focal infection and develop enlargements of the thyroid, whether becoming toxic or not, I am not free to believe that infection alone, nor the infective agent, causes goiter. The presence of infected teeth, or infected hypertrophied tonsils, or contagious diseases, or other infections will cause in thyroid patients, thyroiditis, enlargements of adenomas, or toxic symptoms, occasionally. The infective agent very rarely does this directly, but the focal toxemia causes a secondary effect on the thyroid. The weight of evidence and observations leads me to conclude that except for a direct thyroiditis, which is not uncommon, thyroid enlargements or thyroid zones are not caused necessarily by direct infective agents. This is said with due respect to the modern writers on the subject who lean toward some infective agent in itself being responsible for thyroid zones. The future will settle the question whether direct infection, or intestinal toxemia, or just the lack of some element in the soil or water, or uncleanliness in the handling of vegetables grown here is, or contains, the causative agent.

The large numbers in our section who are practically normal and healthy otherwise, those who lose their enlargements of the thyroid during absence from this section, and the presence of enlargements which become more marked here than elsewhere during the periods of life when the greatest metabolic changes occur—as puberty, menopause, menstruation and pregnancy— are points in circumstantial evidence that offset much in the infective theory.

Sasaki and McCarrison's experiments with the addition of sublimated potassium iodid in a dilution of 1:5,000,000 to rat feces contradict rather than strengthen the infection theory.[5]

The arguments of Kutschera and Taussig can be explained as easily by soil and water supply in susceptible persons.[6] D. Marine and his associates have done work that is most interesting and instruc-

5. Crotti: Thyroid and Thymus, 1918, p. 264.
6. Crotti: Thyroid and Thymus, 1918, p. 265.

tive.[7] They have found that reduction and prevention of thyroid enlargements can be obtained by the use of 2 gm. of sodium iodid taken in 0.2 gm. doses for ten days twice yearly.[6]

In the families who live here constantly, where there is crowding and plainer, simpler methods of living and poorer hygienic conditions, goiters are more prevalent. This observation has been made elsewhere and corroborated many times.

CONCLUSIONS AND SUMMARY

1. It must be recognized that in a zone in which thyroid enlargements occur, as here, there is a normal physiologic hypertrophy, and this should not be called goiter. But to appreciate the various lines of demarkation, much study and astuteness in the differential diagnosis of thyroid enlargements is needed. All adenomas, cystomas and distinct colloid goiters can be classed as nonphysiologic. Simple enlargements may be only a physiologic response to internal needs or external influences,—the latter exaggerating the former. The thyroid gland, no doubt, plays an important rôle in the endocrine hormone in maintaining the balance of metabolism in the body and being prominently located, exhibits its response more markedly than do its associates. But it must be remembered that long continued hypertrophy means permanent enlargement, and one must always keep in mind the definite pathologic potentiality of this most active tissue. When hyperplasia occurs in simple goiter, or adenoma, whether fetal or adult, true exophthalmic goiter and hyperthyroidism may follow. I need not mention the vital organ degenerations that mark their paths.

2. One thousand seven hundred and eighty-three persons, ranging in age from new-born to 61 years, were examined for enlarged thyroids. One thousand one hundred and forty- six had enlarged thyroids with 682 simple goiters, 420 adenomas and cystomata and 44 colloid.

3. The incidence curve shows that goiters increase in both sexes during puberty, dropping to a small degree after the growth of the individual is attained. The curve remains in the female for the child bearing period, going down at about 38 or 40 years, when it rises again for the menopause. In the male, the curve gradually drops till 35 or 40 years, when there is a small rise due to the growths in the glands asserting themselves, the male having no special metabolic change to influence the enlargement.

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7. Kimball, Rogoff and Marine: The Prevention of Simple Goiter in Man, J. A. M. A. **73**:1873 (Dec. 20) 1919.

4. Charts 1 to 6, inclusive, demonstrate the occurrence by age and sex of the various relationships of simple goiter, adenoma and cystoma, respectively.

5. The simple goiters maintain the high percentage till 35 years is attained and the adenoma and cystoma sustain the height of the incidence curve after that age.

6. The liability table given is approximately accurate.

7. The various water supplies—spring water or Lake Superior water—influence the enlargements of the thyroids the same.

I wish to thank Mr. H. C. Kenny and assistants for their services on the charts.

VARIATIONS OF ACID CONCENTRATION IN DIFFERENT PORTIONS OF THE GASTRIC CHYME, AND ITS RELATION TO CLINICAL METHODS OF GASTRIC ANALYSIS *

FRANK D. GORHAM, M.D.
ST. LOUIS

The quantitative determination of the variation of gastric acidity during different phases of digestion by the so-called "fractional method of gastric analysis" is presumably based on the assumption that the gastric chyme, after a test meal, is a homogeneous mixture, and that a small portion (from 6 to 10 c.c.), aspirated at fifteen minute intervals, represents the acid concentration of the gastric contents as a whole at that period of digestion. If this above hypothesis is correct, and if it is based on a true physiologic principle, then we should expect the acid concentration of different portions of the remaining gastric chyme to be similar at these different intervals after a test meal. It is my purpose to show that this hypothesis is not based on true physiology, and that the acidity of one portion, as obtained by the fractional method, may differ widely from the acidity of different portions of the remaining contents.

METHOD OF PROCEDURE

After the removal of the fasting contents of the stomach by means of a small, soft stomach tube of the Rehfuss type, the patient is given the Dock test meal, consisting of 30 gm. of dry shredded wheat biscuit and 400 c.c. of water. The tube is then reintroduced forty-five minutes after the meal, and the contents aspirated in 10 c.c. portions in rapid succession until the stomach is empty, the last portion being obtained after the inflation of the stomach with air, the patient lying supine. The acidity of these different portions is determined separately by the Toepfer method of analysis, titrating with tenth normal sodium hydroxid, using dimethylamidazobenzol and phenolphthalein as indicators. Tenth normal hydrochloric acid is used for hydrochloric acid deficit. An equal mixture of all samples is used for determining "the average acidity."

This method is practical and is considered sufficiently accurate for our purpose. Considerable care must be taken in preventing the patient from swallowing saliva, and also from extreme retching during the withdrawal of the gastric contents. Samples containing excess of mucus or of bile should not be used for the examination.

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RESULTS OF EXPERIMENTS

In my experiments the above method of extraction and analysis has been used in sixty-five cases with varied clinical diagnoses. In a few cases successive test meals were given, and the stomach was completely emptied at ½ hour, 1 hour, 1½ and 2 hours: in the remaining cases the contents were removed at forty-five minutes after finishing the meal. In 73 per cent. of these patients the acidity of the first sample varied considerably (from 20 to 102) from the acidity of the

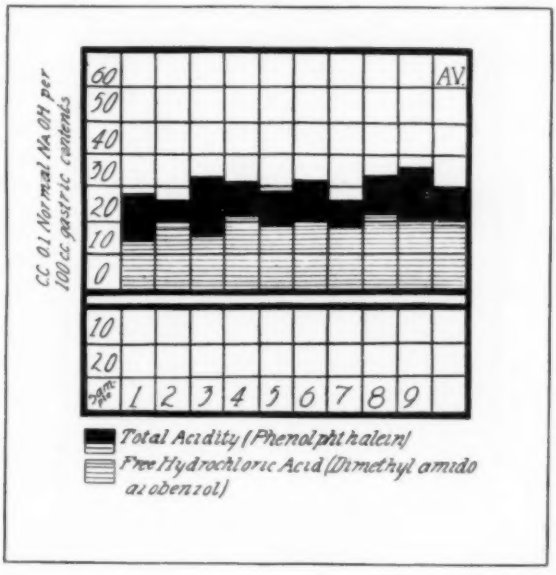

Fig. 1.—Clinical Diagnosis: Constipation. Notice the slight variation of acidity of the different portions of the gastric chyme aspirated in 10 c.c. portions in rapid succession forty-five minutes after a test meal consisting of 30 gm. shredded wheat biscuit and 400 c.c. water.

successive portions. For example, in a patient without clinical evidence of disease (Fig. 1), the acidity of the first sample obtained varied little from the acidity of the successive ones. This, however, is in marked contrast to the results obtained (Fig. 2) in a patient with a perforating duodenal ulcer (twelve hours before operation), where only a trace of free hydrochloric acid was obtained in the first sample at forty-five minutes after a test meal. One of the successive portions (Sample 11) showed a total acidity of 118 and a free hydrochloric acid

of 106. The average of all samples was total acidity, 66; free hydrochloric acid, 55.

It is interesting to note that in a case of supposed achlorhydria (Fig. 3) free hydrochloric acid appeared only in one sample. The other samples, and an equal mixture of all samples, showed a free hydrochloric acid deficit.

In a case of benign pyloric stenosis, successive test meals were given, and the gastric contents were removed in 10 c.c. portions by the above method ½ hour, 1 hour, 1½ and 2 hours after the meal. The

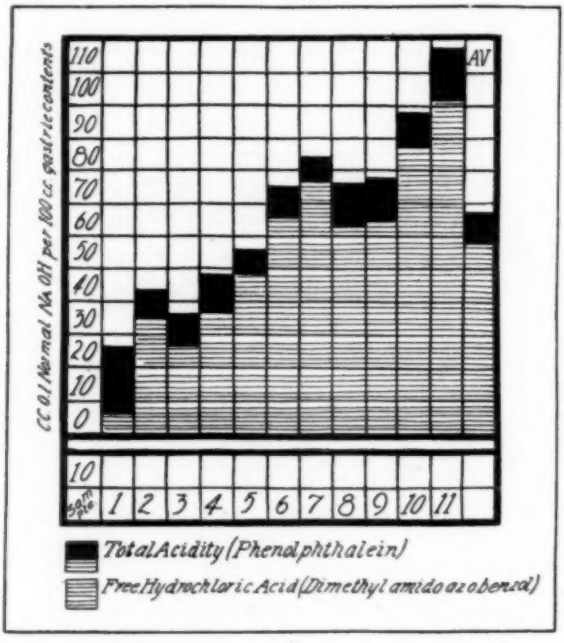

Fig. 2.—Clinical Diagnosis: Perforating duodenal ulcer (confirmed at operation). Stomach emptied by aspirating 10 c.c. portions in rapid succession forty-five minutes after a test meal consisting of 30 gm. shredded wheat biscuit and 400 c.c. water. Notice variations between "sample" (sample 1) usually obtained by the "fractional method," the high point of acid concentration (sample 11) and the average acidity of all samples (last column).

variations of the acidity of different portions of the chyme at these different periods was definite; and if we chart (Fig. 4) the low total acidity at these different periods as one curve, and the high total acidity as another curve, it will be seen how great a variation can be accounted for by the unequal acidity of different portions of the gastric chyme.

REVIEW OF LITERATURE

Pavlov,[1] in considering the movements of the stomach, was of the opinion that "the contents of the greater stomach remain for hours unmixed, and that the gastric juice digests and dissolves the mass from the exterior inwards."

According to Cannon,[2] a stratification is produced which remains throughout the greater part of digestion, the mass being acted on by the gastric juice from the periphery inward. In consequence, the interior remains long unacidified and here salivary digestion may continue for hours.

Grutzner[3] fed various animals with food, the successive portions of which were of different colors. At varying intervals the stomachs were tied off, removed and plunged into a salt and ice mixture; the mushy contents were frozen solid and cut into sections, always showing a definite stratification.

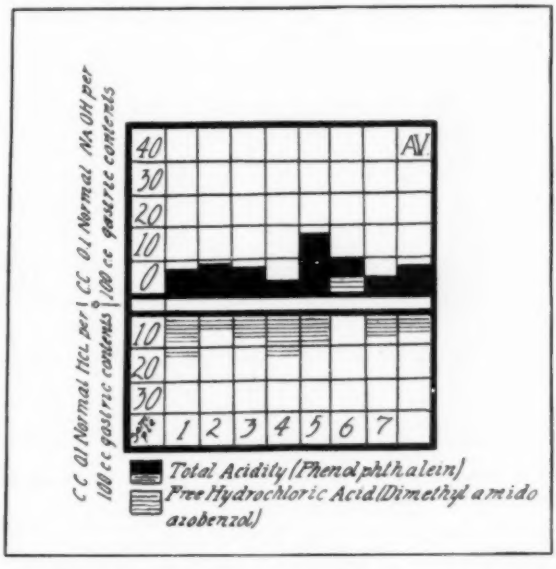

Fig. 3.—Clinical Diagnosis: Chronic Gastritis. Stomach completely emptied by aspirating 10 c.c. portions in rapid succession forty-five minutes after a test meal consisting of 30 gm. shredded wheat biscuit and 400 c.c. water—all samples except one (sample 6) and a mixture of all portions show a free hydrochloric acid deficit (last column).

Prym[4] investigated the behavior of a liquid meal, using Sahli's flour and butter soup. Dogs were given the soup to which blue litmus had been added, and at varying intervals the stomachs were tied off, frozen solid and cut into sections. The central portion and that near the cardia were usually found blue

1. Pavlov: The Work of the Digestive Glands, Ed. 2, London, 1910, Charles Griffin & Co., p. 182.
2. Cannon: The Mechanical Factors of Digestion, London, 1911, Edward Arnold; New York, Longmans, Green & Co.
3. Grutzner: Arch. f. d. ges. Physiol. **106**:463-522, 1905.
4. Prym: Deutsch. Arch. f. klin. Med. **90**:310 (June) 1907.

in color, the rest having been turned red by the hydrochloric acid. Different portions of these contents were cut out and the acidity was determined. It appeared that the degree of acidity was greater at the periphery of the mass than at the center. Prym also administered the liquid meal to a number of patients, and expressed the stomach contents through a double tube with one opening at the tip and the other 10 cm. higher up. In this way he was able to obtain gastric contents simultaneously from different parts of the stomach and found that the two portions varied widely in acidity.

Sick,[5] by a similar method, found that in man, after a liquid test meal (Sahli), the acidity of the pyloric gastric contents varied much from that of the fundal portion: and that, therefore, even after a liquid meal, the stomach contents are far from homogeneous.

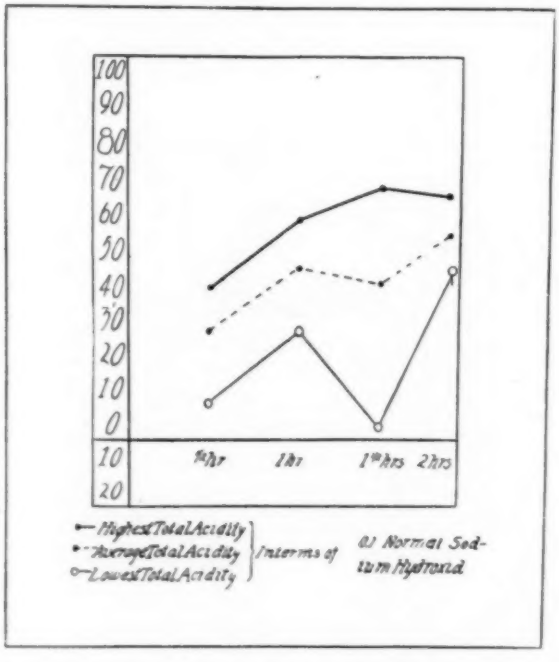

Fig. 4.—Clinical Diagnosis: Pyloric stenosis, benign. The upper curve shows the high total acidity; the lower curve shows the low total acidity, and the broken line the average total acidity of the gastric chyme aspirated in 10 c.c. portions in rapid succession at ½, 1, 1½ and 2 hours after successive test meals consisting of 30 gm. shredded wheat biscuit and 400 c.c. water.

Taussig[6] gave a number of patients test meals and at one hour obtained all the contents possible in the erect posture, and then expressed a portion of the remainder after inflating the stomach with air, the patient lying "prone" or nearly so. The acidity of these two portions was then determined and com-

5. Sick: Ibid. **88**:169 (Oct.) 1906.
6. Taussig and Rush: Boston M. & S. J. **158**:79 (Jan. 16) 1908.

pared. He found that in a majority of instances these two portions varied in the degree of acidity. In some of the cases the difference was excessive; for instance, in a case of suspected gastric ulcer the first portion of 65 c.c. had a total acidity of 103 with free hydrochloric acid 76, while the second portion of 50 c.c. had a total acidity of 52 and free hydrochloric acid 26.

DISCUSSION

It has been shown by the result of experiments, and the work of others, that different portions of the gastric chyme may vary widely in acid concentration: and, therefore, a small sample as obtained in the "fractional method of gastric analysis," or in other methods, where only a small portion of the contents is obtained for analysis, is not, in the majority of instances, representative of the gastric chyme as a whole because the acid concentration of this portion may vary considerably from the highest or lowest acidity of some remaining portion, or the average acidity of the entire gastric contents at that period. The "sample" obtained by the "fractional method" only represents the acidity of the gastric chyme at that moment, in the part of the stomach from where it is obtained; or, in other words, it is dependent entirely on the position of the tip of the tube in the stomach. This position is necessarily a constantly changing one, due, first, to the change of size and position of the stomach while emptying itself through the pylorus and by aspiration; second, the shortening and lengthening of the stomach from gastric contraction; third, the peristaltic waves that tend to carry the tube toward the pylorus.

This explains, in part, the great variety of acidity curves obtained by the "fractional method" in the normal and similar pathologic conditions that in the past have been attributed to secretory variations. What has been said concerning the "fractional method" also applies to all other methods of gastric analyses where only a sample is obtained after a test meal. Therefore, in order to speak of quantitative gastric analysis, the stomach must be emptied completely at a definite time after a standard test meal. The true fractional analysis necessitates the giving of successive test meals and extracting them at different periods: and this, in the majority of instances, is impractical in clinical work.

CONCLUSIONS

1. A method of gastric analysis is introduced for determining the variations of acid concentration in different portions of the gastric chyme after a test meal.

2. Experimental evidence is given to show that the gastric chyme is not, in the majority of instances, a homogeneous mixture after a test meal, and that the acidity of different portions may vary widely.

3. In the so-called "fractional" or other methods of gastric analyses where only a small sample is withdrawn, the small portion removed may or may not be representative of the gastric contents remaining in the stomach.

4. Attention is called to a physiologic principle that explains in part the great variety of curves obtained by the "fractional method" in the same individual and in similar pathologic conditions which in the past have been attributed to secretory variations.

I desire to express obligation for the technical assistance of Miss Bertha Isaacs.

THE NATURE OF SPECIFIC HEMOLYSINS AND A STANDARD METHOD OF PREPARING ANTISHEEP HEMOLYSIN *

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From the time of the discovery of specific antibodies and their subsequent application to the so-called complement fixation tests, the study of specific hemolysins has especially attracted the attention of numerous investigators.

As early as 1875, Landois,[1] in the course of transfusion experiments, noticed the toxic (hemolytic) effect of alien serums on the erythrocytes of the recipients. But our knowledge of specific hemolysins dates back to 1898, when Belfanti and Carbone,[2] and almost simultaneously Bordet,[3] published their observations on the gradually acquired hemolytic properties of serums of animals injected with erythrocytes of other species.

Following the above observations, more important facts about the multiplicity of such lytic antibodies were disclosed, and so, the general interest was more concentrated on bacteriolysins and other kinds of cytolysins that have to do more directly with the all important question of immunity and anaphylaxis. This resulted in a partial neglect of the equally important question of the nature and mode of production of specific hemolysins.

Hemolysis, in general, is the term applied to the solution or lysis of red blood corpuscles. The term should be applied to some sort of alteration of the red cell stroma permitting the hemoglobin to escape into the surrounding fluids. The stroma may or may not be disintegrated. As this article deals only with specific hemolysins, the question of nonspecific hemolysis brought about by any one of the physical or chemical agencies, such as heating, freezing or thawing, effect of hypertonic or hypotonic solutions, toxins, either bacterial or vegetable, etc., lies outside its scope. Therefore, we shall confine ourselves to specific hemolysins produced under biologic methods by parenteral introduction of alien erythrocytes.

The various methods employed in the production of specific hemolysins are, either in part or as a whole, a repetition of the original method of Bordet, with only a few variations of the dose, of the interval between injections, and of the choice of the site for parenteral introduction of alien erythrocytes. These variations were necessitated by

* From the Department of Laboratories, Beth Israel Hospital.

1. Landois: Die Transfusion des Blutes, Leipzig, 1875.
2. Belfanti and Carbone: Giorn. della Acad. di Torino, July, 1898.
3. Bordet, J.: Sur l'agglutination et la dissolution des globules rouges par le sérum d'animaux injectés de sang défibriné, Ann. Inst. Pasteur **12**:688, 1898.

the difficulty of producing certain hemolysins, such as antihuman hemolysins. A real step toward the understanding of the nature of such hemolysins was taken when washed red cells, instead of whole blood, were injected. This was a logical sequence to our knowledge, that the whole blood was not a simple antigen. Whole blood, besides the various formed elements in it (which by themselves are compound proteins) contains serum, serumalbumin and serumglobulin.

The most generally adopted method of producing hemolysins (antisheep, for complement fixations reactions) is by intravenous injection of sheep cells into rabbits, the amounts varying from 1 to 2 c.c. of a 50 per cent. suspension until four or five such injections are successfully administered, and about a week after the last injection, testing the rabbit serum for hemolysins. The interval between injections varies from three to four days. This method has found general acceptance in the majority of our biological laboratories.

By injecting washed erythrocytes, the possibility of production of undesirable serum antibodies of the nature of serum precipitins has been greatly reduced; but erythrocytes are not a simple antigen, as they are commonly thought to be. Histologically, erythrocytes are composed of a colorless envelope enclosing a solution of hemoglobin. The envelope represents the cell protoplasm and its chemical nature is mainly lipoidal. It is soluble in ether, chloroform and other similar fat solvents. The hemoglobin is a conjugate protein composed of globin, a protein of the group of histons, and hematin, the iron containing pigment. Although the mammalian erythrocyte is devoid of a nucleus, still it contains small traces of nucleoprotein in addition to the above mentioned ingredients.

The relative proportion of the different ingredients is shown in Table 1 taken from Abderhalden (cited after Hammarsten).

TABLE 1.—Various Ingredients of Erythrocytes

1,000 Parts Contain	
Water	688.00
Organic solids	303.88
Inorganic solids	8.12
100 Parts of the Dry Organic Matter Contain	
Protein	5 to 12 parts
Hemoglobin	86 to 94 parts
Lecithin	1.8 parts
Cholesterin	0.1 part

With such a complex antigen as the erythrocyte, the question naturally arises as to what ingredient is mainly or solely responsible for the production of hemolysin. Ehrlich and Morgenroth [4] produced

4. Ehrlich and Morgenroth: Ueber Haemolysine, Berl. klin. Wchnschr. **21**: 453, 1900.

hemolysins by injecting laked sheep blood to goats. Bordet and Von Dungern maintain that the stroma is the exciting agent. Bang and Forssman [5] were able to produce hemolysins by injecting animals with ether extracts of red blood cells. Nolf attributes mainly to hemoglobin the production of hemolysin, while the stroma, according to him, give rise to hemagglutinins. In a recent study, Kolmer and A. Rule,[6] in corroboration with Vedder [17] were able to produce antihuman hemolysins by injecting washed human cell stroma into rabbits.

EXPERIMENTAL WORK

We separated the complex antigenic value of the erythrocyte into its component parts and then investigated each part individually. As it is possible to separate the stroma from hemoglobin—the major antigenic fraction represented in an erythrocyte—the following, rather simple technic, was developed.[8]

After washing sheep cells absolutely free of serum (this takes at least five or six washings in physiologic sodium chlorid solution), the supernatant saline solution was decanted and replaced gradually with sterile 0.4 or 0.5 per cent. saline solution, shaking constantly, until enough hypotonic saline solution was added to hemolyze almost completely the red cells. A few cells should always remain unhemolyzed in order to protect the further destruction of the already hemolyzed cells. These few undissolved red cells are gotten rid of by a few turns in the centrifuge and the opalescent red fluid is decanted free of undissolved red cells. It contains, in suspension, the cell envelopes or the so-called "shadow forms," with some leukocytes in a menstruum of hemoglobin solution.

To separate the stroma from hemoglobin, the opalescent fluid obtained was further centrifuged at a very high speed for 30 minutes until the supernatant fluid was absolutely transparent. Now, the tube showed at its bottom a small amount of a flesh colored mass; this represented the stroma. The fluid portion was decanted and the sediment shaken repeatedly with physiologic sodium chlorid solution and centrifuged until it was free of all the traces of hemoglobin. Finally, the uniform emulsion was made in saline solution of an equal

5. Bang and Forssman: Untersuchungen über die hämolysinbildung, Zentralbl. f. Bakteriol. u. Parasitenk. **40**:151.

6. Kolmer and Rule: Studies in the Standardization of the Wassermann Reaction, Am. J. Syphilis **4**:484, 1920.

7. Vedder, E.: The Production of Antihuman Hemolysins, J. Immunol. **4**: 141, 1919.

8. Vedder [7] noticed that by passing ordinary illuminating gas through washed erythrocytes, a larger percentage of cell envelopes, 33 per cent., could thus be obtained. As our work antedates that of Vedder, we will give our technic as adopted three years ago.

volume with that of the original blood used. This was placed in a sterile flask and kept aseptic with the addition of a little phenol, enough to make a 0.5 per cent. solution. This constituted the stock antigen of the lipin fraction of erythrocytes.

The hemoglobin fraction was further diluted with saline solution to five times its original volume and centrifugalized repeatedly for from one half to one hour until it was free of all formed elements, when examined microscopically.[9]

After thus separating the two main antigenic fractions of the erythrocyte, the following three series of experiments were undertaken:

Series A, to show the antigenic value of each fraction by itself.

Series B, to show the anaphylactic or toxic value of either fraction.

Series C, to inquire into the possibility of nonspecific toxicity on the part of either fraction.

EXPERIMENT SERIES A

Lipin Fraction.—To test the antigenic value of the lipin fraction both rabbits and guinea-pigs were used. These animals were injected at regular intervals of two or three days with amounts of stroma to represent from 5 to 10 c.c. of 50 per cent. erythrocyte suspension until four or five such injections had been administered successfully. A week from the last injection, animals were bled to death, no anesthetic having been used for this purpose. The serum thus collected was tested for the following antibodies:

1 Agglutinins and Precipitins: To test for agglutinins and precipitins, of the various dilutions of immune serum shown in the table below, each tube contained 0.25 c.c. and in addition 0.25 c.c. of 1 per cent. washed sheep cells suspension. The tubes were shaken well and incubated at 37 C. for one hour, then left at room temperature and the readings were taken the following morning.

2. Hemolysins: Here, again, of the various dilutions of immune serum, each tube contained 0.10 c.c. to each 0.10 c.c. of 5 per cent. washed sheep cells and the volume of each tube brought up to 0.50 c.c. by adding saline. The tubes were then incubated in a water bath at 37 C. for thirty minutes. After the cells were thus sufficiently sensitized, 0.25 c.c. of a dilution of guinea-pigs serum representing 2 units of complement was added to each tube. The total volume was brought up to 1.25 c.c. by further addition of 0.50 c.c. of saline. Readings were taken after one hour's incubation in a water bath at

9. It is difficult to get the hemoglobin fraction free of all stroma, for even after a very prolonged centrifugalization, one still finds a "shadow form" in every two or three microscopic fields with the hanging drop method, under 500 diameters.

37 C. The results are tabulated in Table 2. The controls were negative.

3. Hemoglobin fraction: This experiment was carried out only on guinea-pigs. The technic was similar to that used in the lipin fraction experiments. The results are given in Table 2.

TABLE 2.—RESULTS OF EXAMINATION OF IMMUNE SERUM FOR LIPIN AND HEMOGLOBIN FRACTIONS

Agglutinins—Precipitins			Hemolysins		
Serum Dilution	Lipin Fraction	Hemoglobin Fraction	Serum Dilution	Lipin Fraction	Hemoglobin Fraction
1:2	±	++++	1:10	C	C
1:10	—	++	1:50	C	C
1:25	—	+	1:100	C	ACH
1:50	—	±	1:250	C	—
1:100	—	—	1:500	C	—
1:250	—	—	1:1000	ACH	—
1:500	—	—	1:1500	PH	—
1:1000	—	—	1:2000	LH	—

\+ denotes the degree of completeness of reaction.
± denotes doubtful reaction.
— denotes absence of reaction.
C denotes complete hemolysis.
ACH denotes almost complete hemolysis.
PH denotes partial hemolysis.
LH denotes little hemolysis.

The lipin fraction, while almost absolutely lacking in hemagglutinogens and hemoprecipitinogens, is very rich in hemolysinogens. On the other hand, the hemoglobin fraction with a rather marked hemagglutinogen and hemoprecipitinogen shows also a weak hemolysinogen. In our opinion, the presence of such small amounts of hemolysinogens is due not to the hemoglobin antigen but to the unavoidable presence of very small amounts of stroma in suspension in the hemoglobin fraction injected, as already mentioned. If, however, the hemolysins produced by injections of hemoglobin fraction is induced by the specific hemolysin-inciting value of hemoglobin, then its nature should be (although not necessarily) different. This is not, however, the case since the conjoined action of both serums as manifested by hemolysins is represented simply by the sum of their respective hemolytic values as if each acted separately.

EXPERIMENT SERIES B.

Determination of Anaphylactic Value of Each Fraction.—In the course of experiments (series A), it was noticed that animals injected with regulated doses of the lipin fraction never exhibited any toxic reaction to such injections, intravenous for rabbits, or intraperitoneal for guinea-pigs. On the contrary, starting with the third injection,

animals injected with the hemoglobin fraction manifested mild but definite toxic reactions. There were no fatal results either with rabbits or with guinea-pigs. On the supposition that the doses may have been too small to manifest their toxic effects (if at all toxic), a new series of animals was injected with increasing doses of both antigenic fractions, the last injection well exceeding from four to five times the initial dose. Here, again, animals receiving the lipin fraction did not manifest any toxic symptoms. The hemoglobin fraction, on the other hand, manifested varying grades of toxicity, although it was never fatal.

Finally, the original method of Rosenau and Anderson was adopted for producing anaphylaxis. One sensitizing dose of each antigen was injected, and after the completion of the supposed incubation period of approximately twelve days a very large toxic dose, namely, from 10 to 15 c.c. of 50 per cent. erythrocytes, was administered intraperitoneally. Again, the animals injected with the lipin fraction did not manifest any anaphylaxis. On the other hand, the animals injected with the hemoglobin fraction in some cases showed moderately severe anaphylactic symptoms, and in rare instances death occurred.

About two years ago, the question of the cause of sudden death in rabbits injected with sheep erythrocytes for producing hemolysin, was studied. Excluding all cases of death attributable to serum anphylaxis (as a result of improper washing of erythrocytes or to agglutinated masses in the cell suspensions), a certain number of the animals died with definite anaphylactic symptoms on the third injection, from four to six days after the first injection. This is well within the incubation period. In these cases specimens were obtained by biopsy, either while yet under the shock of anaphylaxis or immediately before the heart had ceased to beat, and their serums were tested for hemolysin. The findings were rather interesting. Such serums invariably showed a high hemolysin content as compared with animals that survived a shock or did not manifest it at all. After careful study the conclusion was reached that the degree of toxicity of such intravenous injections was in direct proportion to the degree of previous sensitization of the animal and the amount of erythrocytes injected. The conclusions to be drawn were that death was either the result of true anaphylaxis, where the ratio of the toxic to the sensitizing dose was very much above the normal limits, or that death was due to a simple nonspecific toxic reaction very much like any other chemical intoxication. If the latter hypothesis were true, then the matter could be explained only on the basis of a sudden flushing of the tissue cells with the toxic products resulting from an immediate dissolution of the erythrocytes injected. This aspect of the question is dealt with in the following third series of experiments.

EXPERIMENT SERIES C

Possibility of Nonspecific Toxicity of the Two Fractions.—Many investigators had already observed the nonspecific toxic effects of intravenous hemoglobin injections. The third series of experiments, where very large single doses of both lipin and hemoglobin fractions were injected to sensitized rabbits and guinea-pigs (with the sole aim of determining the minimal lethal dose of these fractions), failed to corroborate the conclusions of previous investigators.

Of the hemoglobin fraction, doses representing 5 c.c. of straight packed cells were injected intravenously, with only transient toxic symptoms, never resulting in death. As regards the lipin fraction, single doses representing over 25 c.c. of straight packed cells were administered both to rabbits and to guinea-pigs with not even the slightest toxic manifestations. It is possible, however, that the different results may be due to a difference in the product used, as this hemoglobin was a rather pure product, free of stroma or of their deterioration products. At any rate, one thing at least is certain, namely, that the toxicity of red cell injections does not reside in the cell stroma; nor are we absolutely certain that it resides in the hemoglobin.

Landsteiner [10] suggested the possibility that in the intact cells the lipin of the envelopes enter into a chemical combination with the protein of the cell, the result being a complex lipinprotein molecule. There is no reason why such a molecule, when acted on by specific lysins and complement, should not result in anaphylatoxins.

Assuming the above actually to be the case, we must then necessarily admit that laking would alter the biochemical composition of the stroma; for, by injecting such stroma into an alien circulation we failed to obtain anaphylatoxins. On the other hand, however, the generous production of specific antibodies is strongly in favor of the view advocating their antigenic value.

Bang and Forssman,[5] working with ether extracts of erythrocytes, state that by injecting such ether extracts into animals they could produce hemolysins. Landsteiner and Dautwitz, however, attribute the production of such hemolysins to other antigenic substances in such ether extracts, either in solution or in suspension.

We have injected into guinea-pigs lipins extracted with absolute alcohol from dried heart muscle. After the administration of from four to five such intravenous injections, covering a period of from

10. Landsteiner: Weichardt's Jahresbericht **6**: 1910.
11. Dautwitz and Landsteiner: Ueber Beziehungen der Lipoide zur Serumhämolyse, Beitr. z. chem. Phys. u. Path. **9**:431, 1907.

fifteen to twenty days, we failed to get any hemblysins in the serums of the guinea-pigs treated.

In all probability, the antigenic value of stroma does not reside in the lipins as such, but, as Landsteiner suggests, in the lipin-protein combination of stroma which may enter into solution or fine emulsion in the organic solvents.

Another explanation of our failure to get anaphylaxis with the lipin fraction of erythrocytes might possibly be found in the assumption of a too vigorous sensitization of the animals with such lipin fractions; as, according to the views of Bordet,[12] the distribution of serum antibodies upon their respective antigens is always uniform. Consequently, where there is an overdose of antigen, the number of antibodies available for each antigen unit will be insufficient to bring about the protein cleavage necessary for the production of poison, that is, anaphylatoxin.[13]

To sum up, whatever be the nature of the hemolytic bodies produced by the injection of cell stroma, the main points to be noted are:

First, that by injecting such products we can produce specific hemolysins similar to those produced by whole washed cells, similar at least as far as their hemolytic value is concerned. In fact, by using such hemolytic sensitizers in thousands of parallel Wassermann tests, uniform results on the whole have been obtained.

Second, that the production of hemolysins in this way is more economical in the use of animals.

Considering the way this sensitizer is produced, we would, naturally, expect that it should be specific for stroma. This means that the complexity of the antigenic value of cells has been done away with. We believe that a sensitizer, produced in the manner explained, will not in any way be inferior to that produced by the usual method, and in addition will give more specific reactions. We might here say that a sensitizer produced by the method in general use, will contain at least two antibodies, antilipin and antihemoglobin. When such a sensitizer is used for complement fixation tests, in the course of hemolysis part of the complement in each test will surely be absorbed by the hemoglobin antibody when the latter is united with its antigen, namely, the hemoglobin now in solution.

I wish to thank Dr. Max Kahn, the director of the Department of Laboratories, for his many kind suggestions during the progress of this work.

12. Bordet, J.: Sur le mode d'action des antitoxines sur les toxines, Ann. de l'Inst. Pasteur **17**:161, 1903.

13. Rosenau and Anderson: A New Toxic Action of Horse Serum, J. M. Res. **15**:179, 1906; also, A Review of Anaphylaxis with Special Reference to Immunity, J. Infect. Dis. **5**:85, 1908.

STUDIES ON THE EFFECTS OF QUININ ON THE LIVER, BLOOD CELLS AND URINE OF RABBITS *

DAVID M. SIPERSTEIN AND MORRIS LITMAN
MINNEAPOLIS

I. EFFECT OF QUININ ON THE LIVER

In the course of a series of observations on the excretion of bile pigments in the duodenum following the use of quinin, Prof. J. P. Schneider [1] found that the bile pigments of the duodenal contents were markedly increased and that urobilinogen also appeared. He regarded this as an indication that the drug gave rise to pathologic changes in the liver. In a search of the literature we have been unable to find reference to any studies on the effect of quinin on the structure of the liver. The present investigation was, therefore, undertaken at his suggestion to determine whether pathologic changes in the liver could be induced in rabbits by the administration of doses of quinin comparable to those given in clinical practice or whether the drug gave rise to hemolysis in vivo.

MATERIAL AND METHODS

For the present investigation, fifteen healthy rabbits were used. Two of them died as a result of the injections and were discarded. With two exceptions, a 2 per cent. solution of quinin hydrochlorid in a Ringer-Langendorf mixture was used. All injections were made intravenously to assure a greater degree of accuracy.

The rabbits were killed by a blow on the head with a heavy stick. The abdomen was immediately opened and pieces of liver tissue snipped off and allowed to drop into a beaker containing a 10 per cent dilution of liquor formaldehydi solution or Carnoy's fluid No. 1. Paraffin sections, cut at 10 microns, were stained with hematoxylin and eosin, and studied. All the material was treated exactly alike.

PROTOCOLS

RABBIT 1 (Fig. 1).—Weight, 1,950 gm.; received no quinin; killed as a control. Normal arrangement of liver cells in cords. Cytoplasm is finely granular, no vacuoles. Pigment granules abundant in liver cells.

RABBIT 2.—Weight, 1,850 gm.; received no quinin; killed as a control. Same as Rabbit 1.

* From the Department of Pharmacology, University of Minnesota.

1. Schneider, J. P.: J. A. M. A. **74**:1759 (June 26) 1920.

Rabbit 3 (Fig. 2).—Weight, 1,680 gm.; received 0.13 gm. quinin (0.079 gm. per kilo); killed one-half hour after injection. Cords of liver cells greatly narrowed, due apparently to pressure of dilated sinusoids. Sinusoids dilated and filled with corpuscles. No pigment granules in liver cells.

Rabbit 4 (Fig. 3).—Weight, 1,850 gm.; received 0.06 gm. of quinin (0.037 gm. per kilo); killed twenty-four hours after injection. Normal arrangement of liver cells. Very little pigment in liver cells. Bile capillaries hard to find. Vacuoles present in the cytoplasm of many cells (hydropic degeneration?).

Rabbit 5.—Weight, 2,260 gm.; received 0.18 gm. quinin (0.079 gm. per kilo); killed twenty-four hours after injection. Liver cells show normal arrangement. Cytoplasm densely granular with small vacuoles. No pigment in hepatic cells.

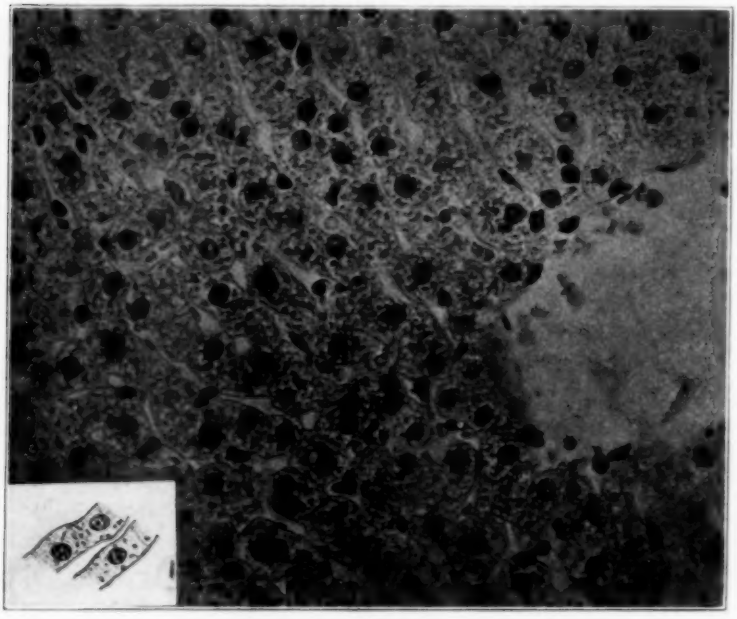

Fig. 1 (Rabbit 1).—Section of normal liver, showing normal structure of cells.

Rabbit 6 (Fig. 4).—Weight, 2,140 gm.; received 0.06 gm. quinin (0.028 gm. per kilo); killed forty-eight hours after injection. Cytoplasm finely granular containing vacuoles of various sizes (fatty vacuoles). Some bile pigment in liver cells.

Rabbit 7 (Fig. 5).—Weight, 1,860 gm.; received 0.07 gm. quinin (0.037 gm. per kilo); killed ninety-six hours after injection. Normal arrangement of cells. Cytoplasm coarsely granular, no vacuoles. Pigment granules abundant in liver cells.

Rabbit 8 (Fig. 6).—Weight, 1,800 gm.; received 0.14 gm. quinin (0.077 gm. per kilo); killed twenty-four hours after injection. Cells have lost their cord-like arrangement. Enlarged liver cells, from three to four times normal in size. Cytoplasm, coarse granules packed at the periphery of cells. Clumps of

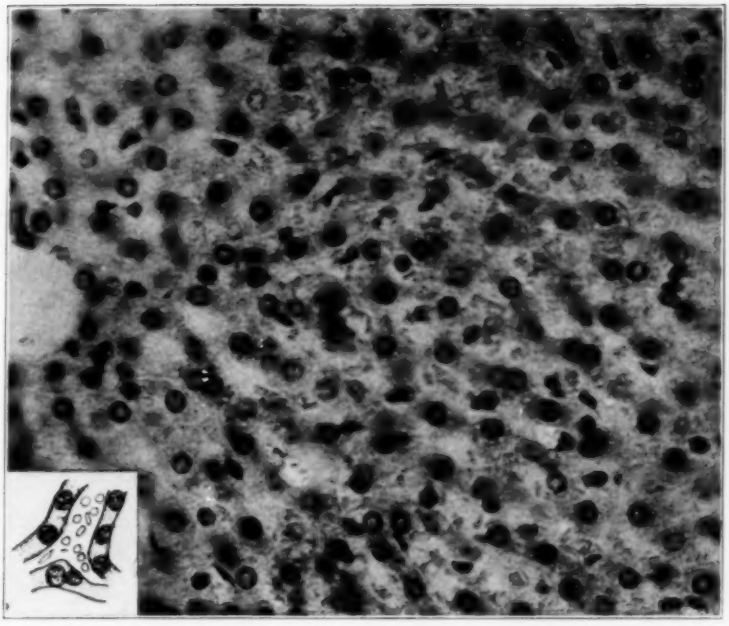

Fig. 2 (Rabbit 3).—Section showing dilated sinusoids and narrowed cords of liver cells.

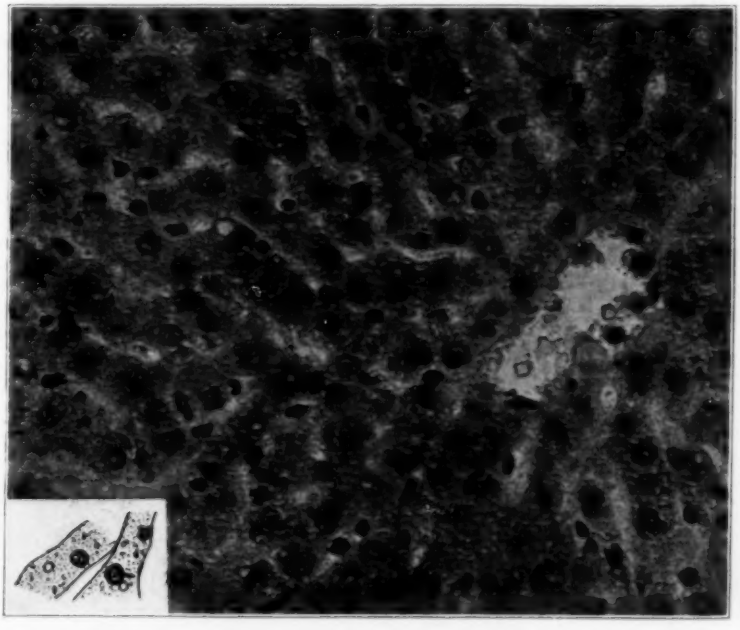

Fig. 3 (Rabbit 4).—Section showing vacuoles in the cytoplasm of many cells (hydropic degeneration?).

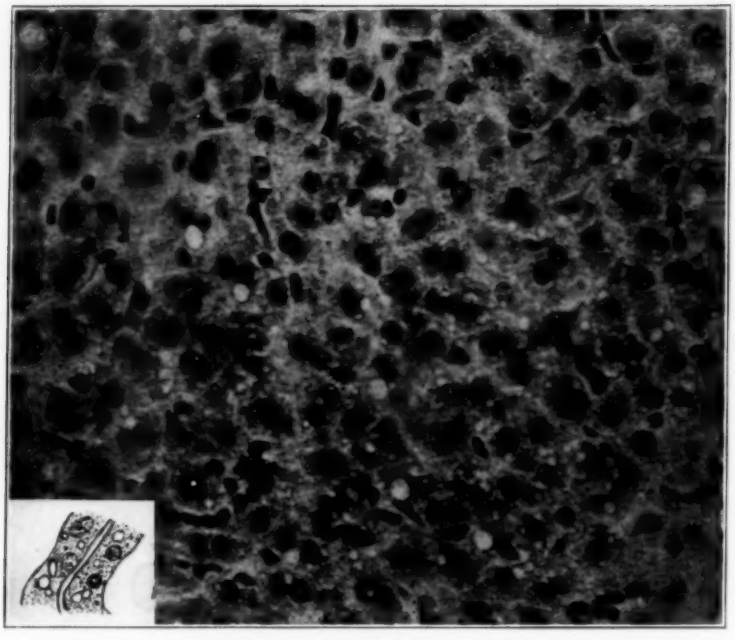

Fig. 4 (Rabbit 6).—Section showing finely granular cytoplasm containing vacuoles of various sizes (fatty vacuoles?).

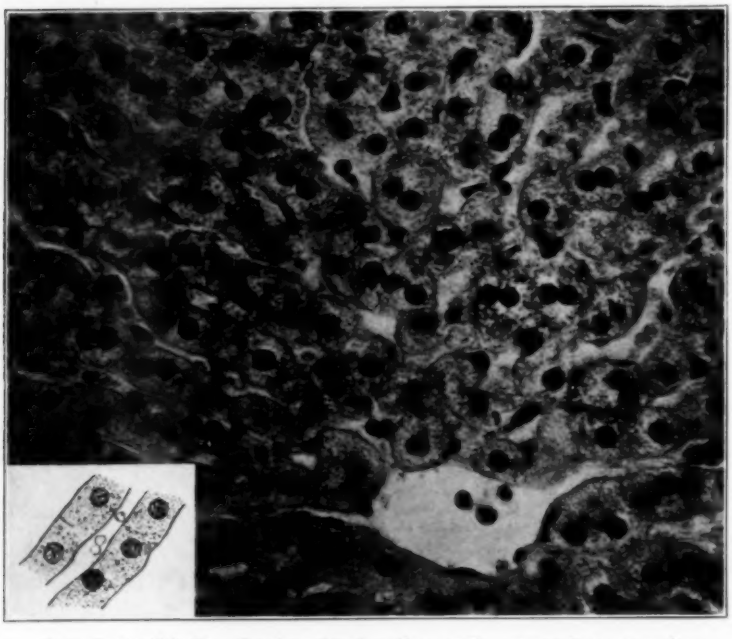

Fig. 5 (Rabbit 7).—Section showing liver cells returned to normal.

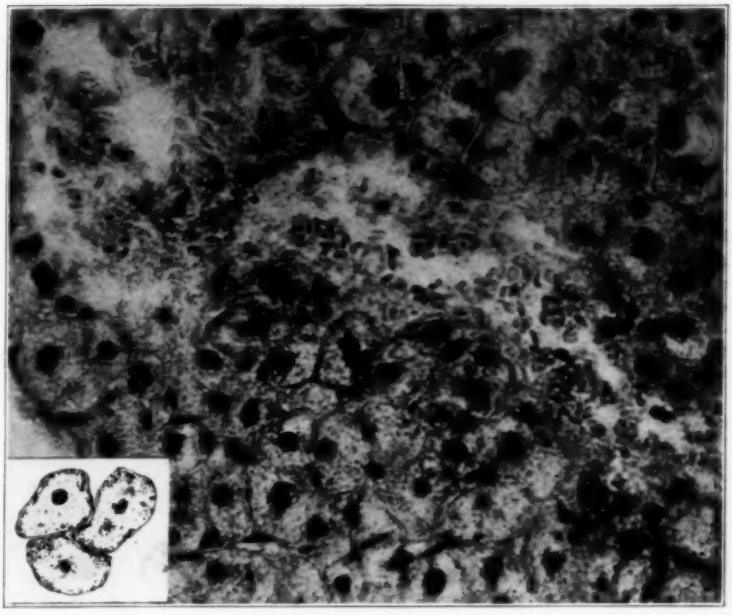

Fig. 6 (Rabbit 8).—Section showing extreme degenerative changes in the cytoplasm of the cells.

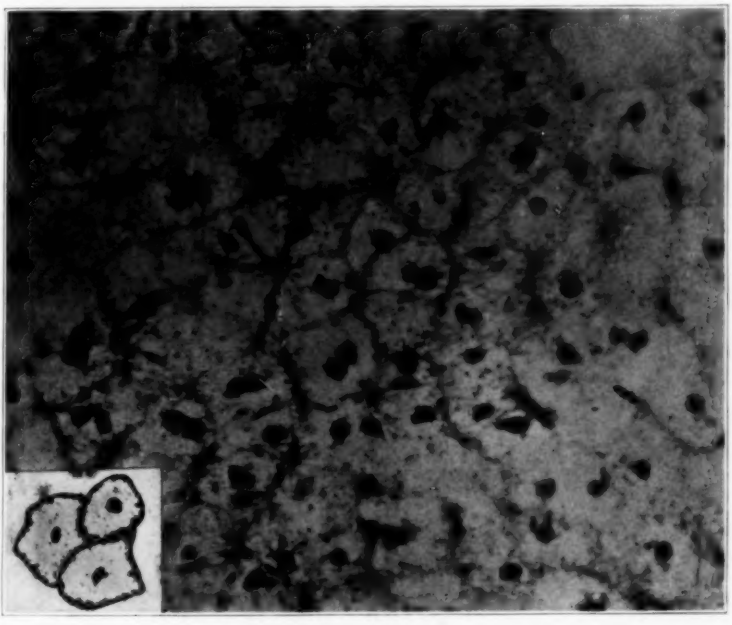

Fig. 7 (Rabbit 11).—Section showing degenerative changes in the cytoplasm of the liver cells.

cytoplasm within the cell. Nuclei, many show pyknotic changes. Sinusoids, difficult to distinguish. The endothelial cells have been pushed together by the enlarged liver cells. Pigment granules not present.

Rabbit 9.—Weight, 2,000 gm.; received 0.12 gm. quinin (0.06 gm. per kilo); killed twenty-four hours after third injection. Same as Rabbit 8.

Rabbit 10.—Weight, 1,380 gm.; received 0.12 gm. quinin (0.087 gm. per kilo); killed twenty-four hours after third injection. Cells retain their cordlike arrangement to some extent. Enlarged liver cells, from three to four times normal in size. Cytoplasm, coarse granules beginning to clump at the periphery of the cell. Nuclei, normal. Sinusoids, variable; normal in some places and difficult to distinguish in others. Pigment granules present. Although treatment was the same as in Cases 8 and 9, this liver was not as markedly affected by the quinin.

Rabbit 11 (Fig. 7).—Weight, 1,450 gm.; received 0.12 gm. quinin (0.082 gm. per kilo); killed 120 hours after last injection. No definite cellular arrangement. Enlarged liver cells (compare with Fig. 6). Cytoplasm, coarse granules packed at the periphery of the cells. Nuclei, show pyknotic changes. Sinusoids, not visible due to the enlarged liver cells. Pigment granules, not present.

Rabbit 12.—Weight, 1,640 gm.; received 0.12 gm. quinin (0.073 gm. per kilo); killed 120 hours after last injection. Same as Rabbit 11.

Rabbit 13.—Weight, 1,720 gm.; received 0.12 gm. quinin (0.064 gm. per kilo); killed 120 hours after last injection. Same as Rabbit 12.

TABLE 1.—Summary of All Protocols

Animal Number	Weight of Rabbit, Gm.	Injection of Quinin, Gm.			Total Amount Received, Gm.	Intervals at Which Quinin Was Injected, Hrs.	Time of Sacrifice of Animal after Last Injection, Hrs.	Total Amount of Quinin per Kilo Body Weight, Gm.	Corresponding Dosage for Man of 150 Lbs. (67 Kilos) Gm.	Comment
		1st	2d	3d						
1	1,970	....	....	....	....	..	...	.....	.....	Normal control
2	1,850	....	....	....	....	..	...	.....	.....	Normal control
3	1,680	0.13	....	....	0.13	..	½	0.079	5.293	No reaction
4	1,850	0.06	....	....	0.06	..	24	0.037	2.479	Mild reaction; recovery in 5 minutes
5	2,260	0.18	....	....	0.18	..	24	0.079	5.293	Mild reaction; recovery in 7 minutes
6	2,140	0.06	....	....	0.06	..	48	0.028	1.876	Mild reaction; recovery in 5 minutes
7	1,800	0.07	....	....	0.07	..	96	0.037	2.479	No reaction
8	1,800	0.06	0.04	0.04	0.14	24	24	0.077	5.159	No reaction
9	2,000	0.04	0.04	0.04	0.12	24	24	0.06	4.02	No reaction
10	1,380	0.04	0.04	0.04	0.12	24	24	0.087	5.829	No reaction
11	1,450	0.06	0.06	....	0.12	96	120	0.082	5.494	No reaction
12	1,640	0.06	0.06	....	0.12	96	120	0.073	4.891	No reaction
13	1,720	0.06	0.06	....	0.12	96	120	0.064	4.288	No reaction

DISCUSSION

One intravenous injection of quinin hydrochlorid produced a gradual progressive change in the liver tissue, followed by a slow recovery. At first, there is noted more or less marked active hyperemia. Within twenty-four hours, the liver cells show some mild hydropic changes in the cytoplasm. In forty-eight, this has progressed to a fatty degen-

eration of the cytoplasm. Apparently, this is the end result and repair commences to take place. Ninety-six hours after the injection, the liver is practically normal again, as far as we can determine.

However, when the animal receives more than one injection of quinin hydrochlorid, the effect is much more severe. The liver cell enlarges and become three or four times the size of the normal cell. All definite cellular arrangement is lost. Cytoplasmic changes are very marked, resembling a granular degeneration. Even the nuclei are affected and pyknosis is common. Sinusoids cannot be made out in many of the sections. The poor blood supply which the cells consequently receive may account for some of the degenerative changes. It is to be noticed that injection of quinin at twenty-four and ninety-six hour intervals apparently gives much the same result.

Quinin hydrochlorid administered intravenously in moderate doses to healthy rabbits produces degenerative changes in the cellular elements of the liver.

II. EFFECT OF QUININ ON THE NUMBER OF BLOOD CORPUSCLES PER CUBIC MILLIMETER

Material and Method.—For these experiments rabbits 7, 8, 9 and 10 were used. Amounts of quinin injected are listed in Table 1. Red and white cell counts were made immediately before and 24 hours after injection of quinin, except rabbit 7, on which counts were made five, twenty-four and ninety-six hours after injection. A differential count was made before and after injection, but there were no variations from the normal and details are therefore omitted from this report. (Table 2).

TABLE 2.—EFFECT OF QUININ ON BLOOD CELL COUNT

Rabbit Number	Dose per Kilo, Gm.	Corpuscles	Blood Counts			
			Before Injection	After Injection		
7	0.037	Red	4,088,000	5 hrs. after 6,032,000	24 hrs. after 6,200,000	96 hrs. after 5,456,000
		White	4,775	8,300	5,960	10,158
				24 hrs. after 1st injection	24 hrs. after 2d injection	24 hrs. after 3d injection
8	0.077	Red	6,090,000	8,080,000	7,970,000	7,250,000
		White	5,275	7,325	7,000	3,000
9	0.06	Red	5,022,000	6,320,000	6,064,000	
		White	3,276	4,075	4,880	
10	0.087	Red	4,728,000	5,176,000	5,980,000	
		White	5,900	6,625	6,100	

Summary.—Within five hours after an injection of quinin we observe an increase in the number of blood cells per cubic millimeter. The increase in leukocytes is nearly proportional to the increase in red

blood cells, as would probably be the case if the polycythemia were due only to a loss of plasma. In spite of the changes observed in the liver, there is no change in the differential count of the leukocytes. This is persistent for the next twenty-four hours, and then declines, so that ninety-six hours after the injection the count approaches the normal. However, after repeated injections the blood count remains high.

III. EFFECT OF QUININ ON THE URINE OUTPUT OF RABBITS

Rabbits 11, 12 and 13 were used. Details of injection were as shown in Table 1. The animals were fed and watered routinely. They were placed in separate cages especially constructed to facilitate the collection of urine with very little loss or evaporation. The urine of each animal was collected for four successive days before the injection then for four successive days after the first injection and for five successive days after the second injection (Table 3).

TABLE 3.—EFFECT OF QUININ ON URINE OUTPUT

Time	Number of Rabbit	Amount of Urine, C.c.					Total, C.c.	Average, C.c.
		1st Day	2d Day	3d Day	4th Day	5th Day		
Before injection.....	11	235	212	212	260	...	949	237
After 1st injection.....	..	336	355	320	288	...	1,349	339.6
After 2d injection.....	..	376	380	280	270	275	1,581	316
Before injection.....	12	236	190	220	230	...	886	221.5
After 1st injection.....	..	400	355	330	340	...	142	373
After 2d injection.....	..	440	312	218	308	236	1,414	283
Before injection.....	13	160	155	124	206	...	645	161.2
After 1st injection.....	..	180	190	196	276	...	892	297
After 2d injection.....	..	176	140	138	died	...	454	151

Injection of quinin into rabbits produces an immediate and considerable increase in the output of urine. This persists for a day or two and gradually decreases. Repetition of the injection produced a similar effect.

SUMMARY

Quinin hydrochlorid, administered intravenously, in moderate doses, to healthy rabbits, apparently produces the following results:

1. Progressive degenerative changes in the liver cells which increase with increasing dosage.
2. A moderate transitory polycythemia rendered persistent by repeated dosage.
3. Polyuria.

We wish to express our thanks to Dr. A. D. Hirschfelder, Director of the Department of Pharmacology, for helpful suggestions and criticism during the progress of this work.

PULMONARY BOTRYOMYCOSIS

REPORT OF A CASE

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ST. LOUIS

Botryomycosis is known to veterinarians as a pedunculated fibrous granuloma of horses especially. The growth usually arises in connection with skin surfaces, and often in the cut spermatic cord following castration. However, in the first description of the condition by Bollinger [1] in 1870 an internal organ, the lung of a horse, was the seat of the disease. In 1897, Poncet and Dor [2] identified the infection in a woman in a small growth on the palmar surface of the hand. Although human cases have been reported from France, Italy and Switzerland, it has been observed most commonly in northern Africa and in Morocco where it is said to occur as commonly as actinomycosis.

The gross lesions consist of abundant chronic granulation tissue which is not especially characteristic but which on microscopic examination reveals granules made up of coccus-like organisms embedded in and surrounded by a hyaline matrix. In the chronic inflammatory lesions described as granuloma pyogenicum or pseudobotryomycosis, these characteristic "botryomycotic granules" are not present.

In 1913, Opie [3] studied a case of hepatic botryomycosis in a girl, 11 years of age, which is the first human case with involvement of an internal organ, and appears to be the only instance of the disease in the United States. In this remarkable case a large part of the liver had undergone necrosis with extensive scarring in some portions and with formation of abscesses containing the characteristic "botryomycotic granules" in others. According to Opie, veterinarians in Missouri and nearby states have seen the disease in horses, while reports indicate that it is uncommon on the Atlantic coast.

In 1914, an article on botryomycosis with a review of the literature to that date was published by Margrou,[4] who was able to reproduce in the testicle of guinea-pigs spherical masses of staphylococci analogous to the "botryomycotic granules" by injection of measured quantities of this organism. The conclusion reached by him is that the zooglea-like hyaline matrix in which the organisms are embedded, and the peculiar

1. Bollinger: Virchows Arch. f. path. Anat. **49**:583, 1870.
2. Poncet and Dor: Lyon méd. **43**:213, 1897.
3. Opie: Arch. Int. Med. **11**:425 (March) 1913.
4. Margrou, quoted by Masson.

cellular reaction, do not signify a specific organism but a certain relationship between the resistance of the host and the virulence of the usual staphylococcus.

Masson,[5] in 1918, observed a case of botryomycosis in a gunshot wound with fracture of the femur. The granulation tissue in which the typical granules are present was curetted from the sinus tract six months after the injury. The wound, after being irrigated with surgical solution of chlorinated soda for two weeks, was curetted and healing followed. He concurs in the opinion expressed by Margrou in regard to the staphylococcus nature of the organism, and places emphasis on nonencapsulated masses of the organisms along the Haversian canals of necrotic sequestrums.

Tussan[6] recently observed four cases of botryomycosis of the skin in Morocco; he discusses them only from a clinical standpoint.

The botryomycotic granules made up of mulberry-like masses of gram-positive coccus-like organisms surrounded by hyaline material are fully as characteristic as the "sulphur" granules of ray-fungus infection, and the histologic diagnosis of botryomycosis is certain and easy. Two views are held in regard to the organism, many regarding it as the usual *Staphylococcus pyogenes aureus,* while others express the opinion that it is a specific coccus. Cultures made from the lesions by the different observers on the ordinary media have usually given a growth quite like that yielded by the staphylococcus.

Especial interest attaches to the case here reported because of its occurrence in the same community from which a previous one with localization in an internal organ was reported.

REPORT OF CASE[7]

A male infant, four months of age, was admitted to the St. Louis Children's Hospital, Sept. 15, 1920. The father is a painter. The father, mother and other members of the family have been well during the life of the child, and there is nothing in the family history to indicate the source of the infection.

The child was born at home and nursed the mother for three months, during which time it remained well. It has been on various artificial foods since being weaned and has had diarrhea at times.

The baby has always had a hacking cough which has been much worse during the past six weeks. About three weeks ago it had a high fever which continued for one week.

Clinical Examination.—The temperature was 99.2 F., respiration 50. The baby seemed quite lively and cried continually in a loud voice. There was a papular eruption over the shoulders which was probably miliariasis.

There was an impaired percussion note over the entire right side and the breath sounds were suppressed and accompanied by fine crackling rales, with

5. Masson: Lyon Chir. **15**:230, 1918.

6. Tussan: Lyon Chir. **15**:241, 1918.

7. The clinical history I have been permitted to use by Dr. Williams McKim Marriott into whose service the case was admitted.

suppressed breathing posteriorly over the left chest. Impression was that of a beginning bronchopneumonia or of an old process clearing up. Examination of heart, abdomen and extremities, negative.

Clinical Course.—September 18, the baby had a distressing cough bringing up a seromucous secretion. The temperature remained low. Leukocytes, 20,000 with 62 per cent. neutrophils. September 23, the lungs showed everywhere medium sized crackling râles. The low temperature is certainly peculiar with so much in the lungs.

October 6 it was evident that the patient was steadily growing worse. Glucose and saline solution were given intravenously. The temperature only occasionally reached 101 F. The lung process had been very peculiar all along—many signs with little temperature elevation. It had been considered of probable tuberculous origin by everyone. Von Pirquet test was repeatedly negative.

The child continued to grow worse and died October 8.

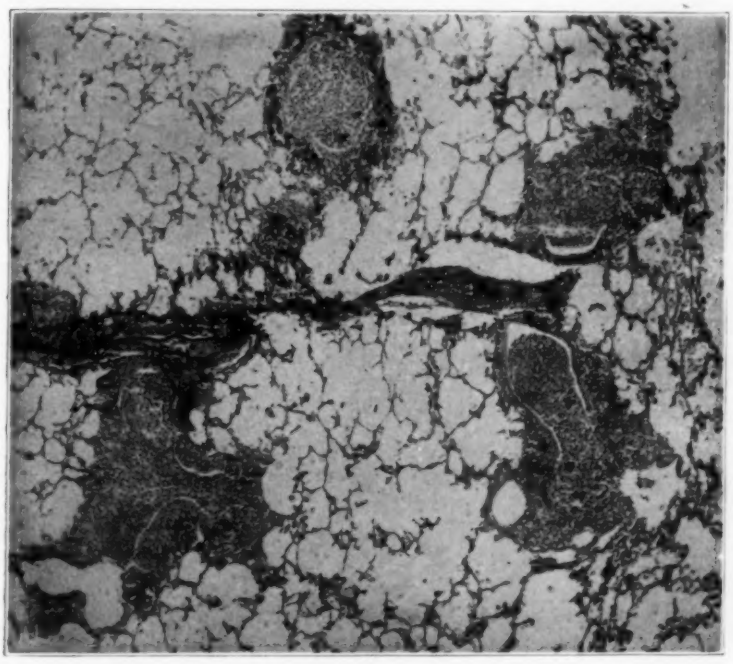

Fig. 1.—A low power photomicrograph to show the areas of bronchopneumonia in which are the dark-staining "botryomycotic granules."

REPORT OF NECROPSY

The body is that of a poorly nourished male infant weighing 2,610 gm. There is slight rigor mortis, no lividity and no demonstrable edema; necropsy three hours postmortem.

The peritoneal cavity contains 200 c.c. clear fluid. The stomach and upper portions of the small intestine are greatly distended with gas.

Gross examination of the organs other than the lungs shows nothing definitely abnormal. The myocardium has a slightly yellowish tinge suggesting some deposition of fat. The spleen is firm in consistency and the lymph nodules may be distinguished. The mucosa of the small and large intestines shows nothing unusual. The pancreas, kidneys, adrenals, genito-urinary organs and aorta appear normal.

Lungs: Each of the lungs weighs 40 gm. On the pleural surface of both lungs there are centimeter areas of a dark bluish color most of which are somewhat depressed below the surrounding pleural surface. These are present in all lobes but are most conspicuous in the posterior portions of the right lung. On section these irregular areas appear to be airless. The bronchi when cut across exude a mucopurulent material distinctly slimy in character. The peribronchial lymph nodes are not especially enlarged.

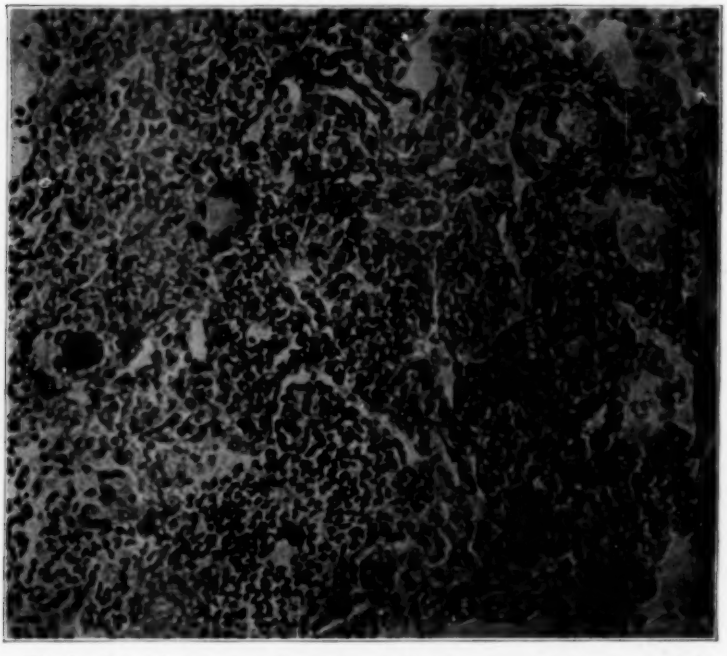

Fig. 2.—A medium power photomicrograph of a pneumonic focus containing two foreign-body giant cells, one incorporating organisms, the other without organisms.

Histologic Examination.—The lesions in numerous sections taken from various parts of the lungs are much alike and consist of areas in which the air sacs are collapsed (atelectasis), and of a bronchitis which in many places involves the entire bronchial wall and extends into the surrounding alveolar sacs (Fig. 1). Even with low magnification the latter lesion is quite different from the usual type of bronchopneumonia owing to the presence of giant cells of the type seen in tubercles and of peculiar dark masses which consist of gram-positive coccus-like organisms embedded in a hyaline eosin-staining matrix. In some instances both within the bronchi and outside giant cell forma-

tion (Fig. 2) has taken place about the groups of organisms so as completely to surround them. In Gram-Weigert stains, where the relation of organism and zooglea-like matrix appears to the best advantage, some of the groups are seen to be surrounded by a rather wide zone of hyaline substance the periphery of which is regular or forms small radial projections; others lie free between the cells with little indication of hyaline about them. However, a small amount of pinkish background is seen about some of the groups of a half dozen or more micro-organisms (Figs. 3, 4 and 5).

The exudate in the alveoli and bronchi consists of endothelial leukocytes and neutrophils in about equal numbers. Many of the former have abundant

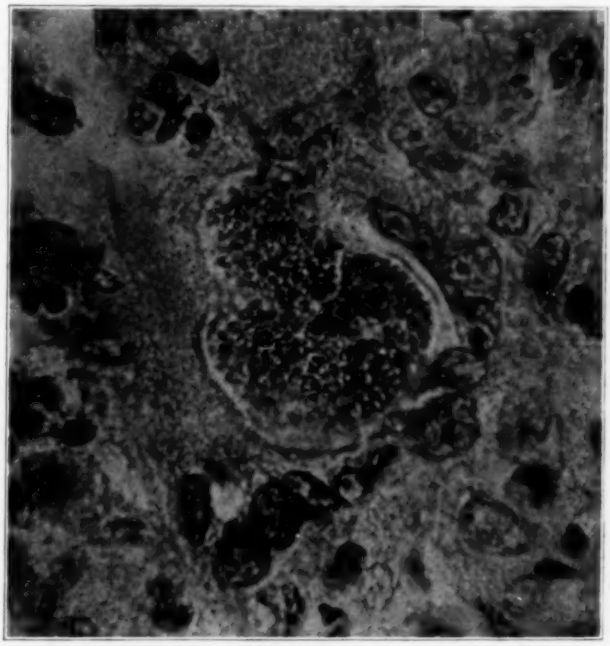

Fig. 3.—Photomicrograph of "botryomycotic granules." Zeiss 3 mm. apochromat. objective and 8 × compensating ocular. Certain ones of the spherical organisms embedded in hyaline are in focus; about the entire mass leukocytes are fusing to form a giant cell.

cytoplasm with fat vacuoles, some have ingested neutrophils, and others have fused to form foreign body giant cells. In the bronchial exudate and in the alveolar sacs there are comparatively few cells of the lymphocytic series but the bronchial walls are the site of an extensive lymphocytic infiltration. In places the epithelium of the bronchi has undergone necrosis and disappeared with extension of the inflammatory exudate into the surrounding air cells. The submucosa of the bronchi is heavily infiltrated with lymphocytes and plasma cells. There are granular foci in the exudate within the bronchi in which most of the leukocytes have undergone necrosis. The alveolar epithelium in the pneumonic areas is intact even in alveoli greatly distended with exudate.

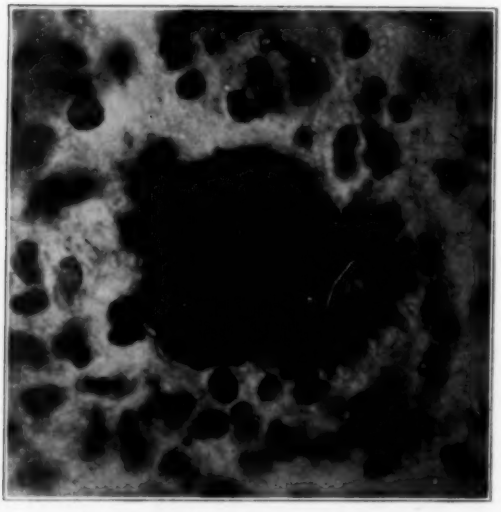

Fig. 4.—The capsule at one side of the mass of organisms stains intensely and presents a radial arrangement.

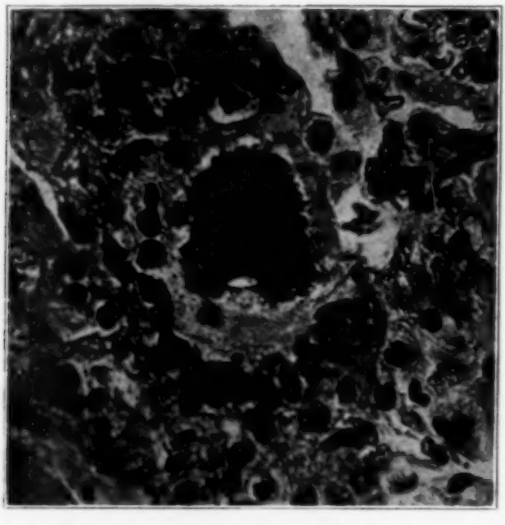

Fig. 5.—Although the homogeneous capsule which lies between the dark mass of organisms and the cells is not stained intensely, it is quite distinct.

The Gram stain of smears of the bronchial exudate made at the time of the necropsy shows further details in regard to the organism. The larger masses of the coccus-like organism are embedded in and frequently encircled by the hyaline matrix, but smaller groups of a half dozen or more often have none of the pink-staining substance about them. There is considerable variation in

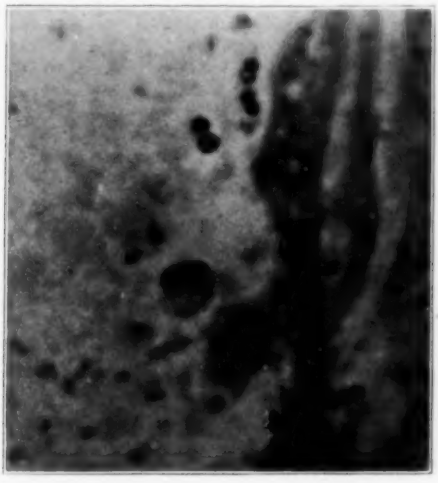

Fig. 6.—Photomicrograph of the organisms in a Gram stain of a smear of bronchial exudate. Zeiss 2 mm. apochromat. objective and 8 × compensating ocular. Three small groups of the organism in one of which the hyaline has been smeared out on one side and stains positively.

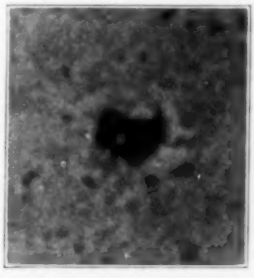

Fig. 7.—A group of the organisms from a part of the smear in which there appears to be a delicate positively staining capsule about each unit of the group. Magnification and staining are the same as in Figure 6.

size and many are less than one-half the diameter of those embedded in the matrix. Groups of two, four, six and eight predominate, and frequently the pairs present a coffee-bean appearance. There are a few chains, the longest consisting of about twenty-four units. In some of the small groups the

hyaline is distinct and about the individual organisms in portions of the smear there are regular pink-staining capsules contrasting with the purplish and more heavily staining organism (Figs. 6 and 7).

Microscopic examination of the other organs reveals no lesions of evident importance. The heart, spleen, stomach and liver are normal. In the mucosa of the intestine there are small collections of plasma cells and an occasional epithelial cell is necrotic and invaded by leukocytes. There is a moderate edema of the kidney with hyaline casts in the tubules. In the intima of the aorta opposite the intercostals the collagen is pushed apart by a small amount of granular material and in this there are a few migrating endothelial leukocytes.

Cultures on blood agar plates made from the bronchial exudate gave a heavy growth of gram-positive cocci which presented the usual appearance of staphylococcus albus. Nothing unusual was suspected at the time of necropsy, and unfortunately the cultures taken had been discarded when the lesion was identified from the sections of lung. Smears and sections of the lung stained by the Ziehl-Neelsen method show no acid-fast bacilli.

SUMMARY

With the pulmonary symptoms predominant at the beginning of the disease and persisting for several weeks in such a manner as to suggest pulmonary tuberculosis, one is led to think that this case was a primary bronchopneumonia which terminated fatally. It is not perfectly clear, however, that this was the sequence of events.

The histologic lesion is that of a typical granuloma and is one not encountered in infections with pyogenic cocci commonly examined microscopically. The zooglea-like matrix likewise is unique. The appearance of the delicate circle of hyaline material about individual organisms which stains positively and is not a retraction zone suggests a true bacterial capsule and, if confirmed by further observations, especially in connection with animal inoculation, would indicate a distinct species of capsulated coccus.

In conclusion I wish to express my indebtedness to Dr. E. L. Opie who brought to my attention the lesion present in his case and to Dr. H. H. Bell for an examination of the cultures.

IDIOPATHIC PURPURA WITH UNUSUAL FEATURES

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Many authorities refuse to regard purpura as a disease entity and consider it merely as a manifestation of some other disease. Its extreme rarity is evidenced by the fact that at the Massachusetts General Hospital there were only sixty-four cases in 155,884 medical and surgical admissions; at Johns Hopkins Hospital there were forty-one cases in 18,594 medical cases, and at the Hamburg General Hospital there were seventy-three cases in 100,000 admissions; B. Ramwell [1] saw sixteen cases among 5,256 ward patients. In his table of 258 cases of all kinds of purpura fifty-four were primary and showed arthritis.

In looking over the literature of purpura, it is difficult to find any mention of familial tendencies in this disease. In fact, familial tendencies have been used as a point against purpura in a differential diagnosis from hemophilia, so rarely are they found. There are, however, a few instances reported to which we must add that of the two brothers in this paper. Cousin [2] describes a family in which the disease occurred in three different branches. A case is described by Dohrn in which purpura was transmitted from the mother to her new-born child. Occurrence of the disease in three sisters is reported by Forster. Wagner reported a case of chronic purpura in which paternal uncle of the patient died of acute purpura hemorrhagica. Bauer also describes familial tendencies to a purpuric diathesis occurring in several members at a certain age. The occurrence of these familial cases of purpura rather speaks for the disease as a definite entity. It would seem that there is in certain families an inherent weakness of the germ plasm which manifests itself either in a deficiency of blood platelet formation or in a primary vascular degeneration, or in both these factors (Duke,[3] Wright and Kennicutt,[4] Deny and Ledingham,[5] and Hess.[6])

1. Branwell: Clinical Studies **3**:325, 1905.
2. Cousin: Ann. de méd. et chir. enf. **17**: (Oct.) 1913.
3. Duke, W. W.: Arch. Int. Med. **10**:445 (Nov.) 1912.
4. Wright, J. H., and Kennicutt, R.: J. A. M. A. **58**:145 (May 20) 1911.
5. Ledingham, J. O. G.: Lancet **1**:1673, 1914.
6. Hess, A. F.: Proc. Soc. Exper. Biol. & Med., 1917.

REPORT OF CASES

CASE 1.—Nelson C.; aged 11; schoolboy; born in Canada.

Family History.—The family history is entirely negative, there being no history of any similar ailment on either parental side, with the exception of the patient's brother whose case is reported later. The father and mother enjoy excellent health. As far back as they can trace, there has never been a bleeder in the family or anyone with hemorrhagic tendencies.

Previous History.—This boy was born normally at full term. He developed normally up to the sixth year after having passed through attacks of measles and whooping cough at the age of 1 year. He had mumps and scarlet fever, complicated by otitis media, at the age of 6. During the whooping cough he would often have epistaxis with paroxysms of coughing but this always stopped promptly and there was never noticed any delay in the clotting of his blood.

The child has been brought up in good surroundings and has had at all times a healthful mixed diet with abundance of fresh vegetables and fruits.

Present Illness.—The present illness began about four years ago with a sudden attack of pain in his elbows. They became swollen, stiff and extremely

Fig. 1.—Elbow joint (Case 1) with area of rarefaction in olecranon process; enlargement of epiphyses of humerus and radius, and roughening of medial articular surface.

tender but not reddened. A similar condition later attacked his knees and from then up to the present he has never been entirely free from trouble in some joint, although the knee joints have been the main sufferers. There has been little, if any, fever with the attacks. The swellings appear quite suddenly and appear to distend the tissues about the joints until they are tense and so tender that the merest touch causes excruciating pain. At first they subsided rapidly and seemed to leave the joint no worse for the attack, but of late the knees have become stiffened and somewhat flexed. Simultaneously, the mother noticed that the child "bruised easily" and showed occasional small hemorrhages into the skin. Also on several occasions there would be a sudden swelling, discoloration, hardness and tenderness of the calf muscles. The boy has never had any involvement of the toes, hips, shoulders, sternoclavicular or temporomaxillary joints. There is no history of hemorrhage from the gums, nose, ears, kidneys, bowels or stomach. His blood clots normally after injury

and he seems normal in every other way, except that he has always been pale. With the exception of the pains in the joints he has no complaints whatever.

Physical Examination.—This reveals a normal sized boy, pale and with a puffiness of the eyelids. The conjunctiva and mucous membrane of the mouth are free of petechiae. The fundi are both clear. There are shotty posterior cervical and inguinal glands. The lungs are clear. The heart is negative, except for a loud systolic murmur over the pulmonic area. The liver, spleen and kidneys are not palpable. The abdomen is negative. The interest centers in the joint condition, especially that of the knee joints. There is great muscular atrophy of both legs emphasizing the enlargement of the knees. The legs are held flexed. The knee joints are both distended, and there is a thickening of the peri-articular tissues. Riding of the patella is demonstrable. The skin over the knees and on the right side, extending down the back of the leg, is tense and of a bluish-yellow hue due to old blood extravasation. The right knee is extremely tender. There is limitation of motion. No crepitation can be elicited. The right gastrocnemius muscle is tense, tender and hard resembling the so-called scorbutic scleroderma. The skin shows a few small purpuric spots with several larger subcutaneous hemorrhages in the various stages of absorption and discoloration. These are mainly in the forearm, elbow and thigh.

Laboratory Examination.—Blood examination shows: hemoglobin, 45 per cent.; red blood cells, 4,000,000; leukocytes, 5,600. Differential count: normal.

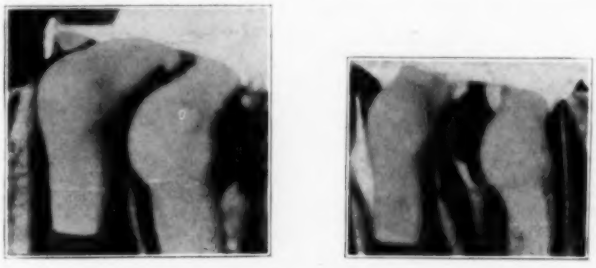

Fig. 2.—Knee joints in Case 1; anteroposterior and lateral views.

The red blood cells show anisocytosis, poikilocytosis, stippling and polychromatophilia. The blood platelet count is 98,039 per c.mm. The coagulation time is normal. The bleeding time is prolonged to ten minutes instead of being from one to three minutes.

The urine is completely negative. The von Pirquet tuberculin test and the Wassermann test are both negative.

Case 2.—Clarence C., aged 15; schoolboy; born in this country. A brother of the patient reported in Case 1. His complaint was "sore elbows."

Previous History.—He was born normally at full term and developed normally. Had attacks of measles, whooping cough, scarlet fever and mumps. Had an attack of jaundice at the age of 5. He had no other acute illness of any kind, and his general health has been good. It was noticed that he "bled easily and freely" on the slightest provocation but no delay in the clotting of his blood was ever present. For instance, on changing altitude, he would suffer with epistaxis, although the changes were not great enough to affect the ordinary person.

Present Illness.—His present illness dates from the age of 5 when he had his first attack of joint trouble. This centered in both ankles, which suddenly became swollen and tender. This condition cleared up rapidly only to reappear after a short interval and then the knees were similarly affected. The

patient was unable to walk. He suffered with these attacks up to the present, although lately they have become less frequent and less severe. For the past three years the attacks have been confined to the elbows and he is able to walk without any difficulty whatever. On one occasion, a diagnosis of purulent arthritis was made and a knee joint was aspirated. Bloody serum was obtained. The boy bruised easily and often had large hemorrhages under the skin. He never had an attack of extensive purpura nor was there ever spontaneous oozing from the gums. Six weeks ago he had an attack of severe colicky pain in the right side in the costo-vertebral region radiating downward and forward over the bladder. To use his words, he "felt something pop inside" and

Fig. 3.—Knee joint of Case 1, lateral view, showing definite area of osteoporosis in epiphysis of femur with undue enlargement; thickening of soft structures of the knee joint, commonly seen in repeated blood effusions. Condylar surfaces are rougher than is the case in normal persons.

then he "felt a hot flush through his stomach." Shortly after he noticed that his urine was bloody and stringy. As soon as he began to pass the blood the pains subsided somewhat. This attack lasted for three days. The urine became clear and the pain disappeared. A similar attack appeared four days ago in the left side. The boy's mother noticed no blood in the urine in this attack which was less severe than the previous one. A microscopic examination, how-

ever, showed the presence of red blood cells. In neither attack was there any purpura, nor did the boy show any melena. There was no nausea or vomiting nor was there any exacerbation of his joint symptoms. There have been no other symptoms of any importance.

Physical Examination.—On physical examination, we find a bright, normal sized, well-nourished boy. He does not appear to be anemic. The head is entirely negative. The eyes show no petechiae. The fundi are clear of any hemorrhages. Mucous membranes are normal. The gums are healthy and the teeth are excellent. There is slight general glandular enlargement. The tonsils are negative. The heart and lungs are clear. The abdomen shows no abnormality. There is marked left costovertebral tenderness present. The liver, kidneys, gallbladder and spleen are not palpable. The skin shows a few large brown and blue bruises, one over the right eye and one near the left

Fig. 4.—Knee joint of Case 1, anteroposterior view, showing small well defined area of rarefaction in epiphysis of tibia. The epiphyseal lines and the shafts of the bones are normal.

elbow. There are a few smaller purpuric spots in the skin of the left forearm. There are no hemorrhages in the muscles.

As in the first case, the interest centers in the joint condition. The left elbow is the seat of an acute process. The joint is very much enlarged and discolored but not especially tender. The bony landmarks are almost obliterated by the effusion into and the distention of the joint capsule. The olecranon process shows as a depression between two large fluctuating bulging sacs. There is limitation of motion in this joint. Both knees are enlarged due to a peri-articular swelling and thickening but they are not tender, there is no limitation of motion nor is there any sign of an effusion at present. There are scars over both knee joints at the site of the previous aspiration. All the other joints are normal.

Blood Examination.—Hemoglobin, 85 per cent.; red blood cells, 4,900,000; white blood cells 6,600. Differential count, normal. The red blood cells were normal. The blood platelet count was 204,000 per c.mm. The coagulation time was normal. The bleeding time was ten minutes. The urine showed a faint trace of albumin with many red blood cells, the remains of the last attack of colic.

The roentgenograms of the joint (Figs. 1, 2, 3, 4 and 5) show, in general, an enlargement of the epiphyses of the bones with well defined areas of rare-

Fig. 5.—Elbow joint of Case 2 showing roughening of humero-ulnar articulation.

faction, small roughening of the articular surfaces, as in osteo-arthritis; and in the knee joint, a definite thickening in the soft structures of the joint such as one sees in bloody joint effusions.

Clinical Course.—The two patients were seen after an interval of seventeen months' army service. The younger brother had had at least one attack of joint trouble a month during this period. He had also had one severe hematemesis in which he lost almost one quart of blood. This occurred six months

after therapeutic intramuscular injections of whole blood. On my return, I found him with a hemorrhage under the tongue, one under the angle of the left jaw, many purpuric spots over the sternum, shins and ankles, and a fresh hemarthrosis of the wrist. His general physical condition was the same, except that the urine showed albumin, casts and red blood cells.

The older boy seemed much improved. Fourteen months after I saw him he suffered a fracture of the right olecranon. He did not know just how or when it occurred. The bone united readily but two months later he developed a fresh hemorrhage in the same joint. He had also had epistaxis but no bleeding into the skin, bowel, stomach or kidney.

A second feature of these two cases is the occurrence of repeated hemarthrosis in each instance. Some even go so far as to doubt its occurrence in purpura, stating that if the arthritic manifestations are at all marked the case should be classed as a simple purpura with arthritis. According to McCrae [7] no case has been found in recent literature. Wagner [8] searched the literature up to 1886 without finding a single case of purpura in which a large hemorrhage had occurred

Fig. 6.—Elbow joint of Case 2.

into a serous sac. Hoffman found no mention of a single definite instance of hemorrhage into a joint in morbus maculosus. There could be no doubt of their occurrence in the above cases. The sudden painful distention of the joints, the external discoloration and subcutaneous ecchymosis of the surrounding tissues and the result of ill-advised aspiration all go to prove the presence of hemorrhage in the joints. The rapidity of recovery of normal appearance and function were also characteristic in the early years of the disease.

A third rare feature is the association of hemarthrosis with the visceral symptoms described under the name of Henoch's purpura or purpura abdominalis. In typical cases of Henoch's purpura joint pains are associated with cutaneous and intestinal hemorrhages and acute nephritis, often of the hemorrhagic type. The arthritis, however, does not go on to the hemorrhagic stage. Each of these two patients, at

7. McRae: Osler-McRae Modern Medicine.
8. Wagner: Deutsch. Arch. f. klin. Med. **39**:431, 1886.

some time in the course of his disease, has shown one or both of these two visceral conditions in addition to joint hemorrhages. Nor is hemorrhage into a joint mentioned as one of the symptoms of peliosis rheumatica by Schönlein in his original description of this condition. This description, although vague, has been taken by most clinicians to include only those cases in which there are fever, malaise, purpura and erythema and joint pains. Barker,[9] however, in his classification of the purpuras, states that often there is hemarthrosis in these cases of Schönlein's disease. The absence of fever, malaise, erythema and pains in

Fig. 7.—Elbow joint of Case 2, posterior view, showing rarefaction in external condyle of humerus.

joints other than those distended by blood, definitely excludes these patients from the peliosis rheumatica group.

Another feature of note is the fracture of the olecranon sustained by the older brother. From the description of the patient this was in all likelihood a spontaneous or pathologic fracture in the neighborhood of a joint that had been the seat of a hemorrhage. If one bears in mind the pathology of this disease, especially with regard to the

9. Barker: Monographic Medicine **3**: p. 239.

rarefaction it effects in the bone substance, it is quite conceivable how this might happen. It might be well, therefore, to consider purpura as a possible etiology for pathologic fracture.

From a perusal of the literature and a consideration of these two cases it would seem that no strict line can be drawn between the various types of purpura described in our modern classification. Morawitz considers all these diseases of the so-called idiopathic purpura group as being different manifestations of one and the same process. Hoffmann, Litten and other German writers have the same view of the primary purpuras, classing them all as "morbus maculosus Werlhofii" of varying degrees of severity. In this group are: (1) *purpura simplex,* with hemorrhages in the skin and subcutaneous tissues; (2) *purpura hemorrhagica,* with hemorrhages of the skin and mucous membranes; (3) *peliosis rheumatica* with cutaneous hemorrhage erythema and joint disease; (4) *purpura abdominalis,* with cutaneous and intestinal hemorrhages and joint pains, and (5) *purpura fulminans,* with cutaneous hemorrhages which run a rapid and fatal course.

The cases here reported partook of features that might allow them to be put in any of the above type, except the last.

The pathology of this condition, when the hemorrhage has been repeated often, is quite interesting. Our knowledge of it has been gained by roentgen-ray study of the living subjects, by operations and by a few necropsies in cases that have succumbed to intercurrent conditions. The hemorrhages occur most often in the knee joint, as trauma is most active here, although other joints may be affected simultaneously.

Following a slight blow or often spontaneously, there develop signs of acute joint affection with joint effusion. The condition may stop here, the effusion be absorbed and the joint heal without change. This, according to the description of König,[10] is the primary stage of the disease. If the effusion persists—secondary stage—it goes on to an inflammation with a fibrinous effusion as in the ordinary tuberculous "white swelling." This condition it simulates almost perfectly, but the roentgen-ray will show that the bone is not involved and that the process is confined to the soft parts of the joint (Love,[11] Carless[12]). In this stage, synovial villae are present as well as defects in the joint cartilages, the changes resembling closely those seen in arthritis deformans or osteo-arthritis. The roentgen ray shows changes in the epiphyseal lines which are zigzag and have a worm-eaten appearance. The condylar outlines are not sharp. The capsule shadow is darkened. There

10. Samml. klin. Vorträge, N. F., Leipzig **36**:233-242, 1892.
11. Keen's Surgery **2**: p. 362.
12. Practitioner **70**:85, 1903.

is bone atrophy with rarefaction of the condyles. Mankiewicz [13] questions whether this is a true osteoporosis or a retrogressive metamorphosis in the architecture of the bony trabeculae. If hemorrhage occurs in a joint often enough, König describes a third stage in which there are contractures, bone and joint changes, thickening of all the periarticular structures and even ankylosis. Ponfick also has described hemorrhages into the bone-marrow. Bowlby [14] thinks these cases resemble osteo-arthritis far more closely than is generally acknowledged. He cannot explain the nodular outgrowths of cartilage, new bone formation, fibrillation of the cartilage matrix and the formation of adhesions all as a result of blood extravasation. The attacks, he states, are different than those exhibited by a healthy patient who is suffering from a traumatic hemarthrosis. He thinks that many bleeders have a special tendency to attacks of acute arthritic inflammation which very closely resemble those of the more severe forms of osteo-arthritis. Barker [15] states that the condition also resembles luetic arthritis.

SUMMARY

Two cases of iodiopathic purpura are described with the following unusual findings:

1. They showed a familial tendency.
2. Repeated joint hemorrhages occurred in both patients.
3. There was an association of joint hemorrrhages with the symptoms of Henoch's purpura.
4. Spontaneous fracture occurred in one case.

13. Mankiewicz: Berl. klin. Wchnschr. **76**:2174, 1913.
14. Bowlby: St. Bartholomew Hosp. Rep., London **26**:77, 82, 1890.
15. Barker: Monographic Medicine **4**: p. 95.

THE PRESENT STATUS OF CARDIODYNAMIC STUDIES ON NORMAL AND PATHOLOGIC HEARTS *

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The experimental or clinical investigator who essays to study circulatory problems that directly concern vital phases of medicine is frequently handicapped because certain fundamental data, which are the key to the interpretation of these problems, are not included in our stock of general information. It is desirable, therefore, first to review briefly some recent experiments which, I believe, help to clarify our understanding of the normal contraction processes in the heart. This accomplished, the laws which govern cardiac behavior will be analyzed. Finally, an effort will be made to see how far these laws may be applied in the interpretation of pathologic conditions with which we are confronted in the clinic.

I. THE FUNDAMENTAL MECHANISMS OF THE HEART RATE

The Physiology of Auricular Systole.—The cardiac cycle is generally described as consisting of auricular systole, followed promptly by ventricular systole and diastole. It has long been known that certain quantitative differences exist between the contraction of the auricular and ventricular musculature. Thus, the greater capacity of the ventricles for performing work and their longer contraction period are generally emphasized, even in elementary physiology. Recently, evidence has been adduced which indicates that qualitative differences also exist. The ventricles receive their impulses through the His-Tawara system in such an ordered manner that all parts of the ventricular myocardium are virtually excited at the same time (Garten [1]; Lewis and Rothschild [2]). Consequently, we may assume that the entire bulk of the ventricular musculature begins and ends its contraction at practically the same moment.

It is different in the case of the auricular contraction. A few years ago, Lewis and his associates demonstrated that the impulses developed rhythmically in the sinus node, spread eccentrically over the atrial muscular tissues, exciting in succession each fractionate portion

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* Lecture delivered before the Harvey Society, New York City, Dec. 11, 1920.

1. Garten: Skand. Arch. Physiol. **29**:114, 1913; Ztschr. f. Biol. **66**:23, 83, 1915.
2. Lewis and Rothschild: Phil. Tr. Roy. Soc. London **206**:181, 1915.

of auricular tissue. In this way, the more distal portions receive their excitation later than those portions more proximal to the cardiac pacemaker.

In 1916, I presented experiments [3] which led to the conclusion that, a short interval after receiving an excitation, each unit of auricular tissue undergoes a brief fractionate contraction lasting about 0.06 second and then relaxes—an interpretation that has recently been confirmed by Lewis and his co-workers.[4] Auricular systole begins with the first fractionate contractions near the sinus node, and ends when a balance of the fractionate relaxations and contractions causes no further decrease in the length of the entire auricle. Since the fractionate units excited first begin to relax during mid-systole, the pressure in the auricles and large veins rises only during the early half and decreases during the latter half of auricular systole. We may therefore divide auricular systole into (a) a dynamic phase, during which blood is injected into the ventricles and (b) an inflow phase, during which some blood actually flows into the auricles from the central veins.

The Consecutive Phases of the Ventricular Cycle.—In order to interpret the dynamic mechanisms of the ventricles, it is sometimes desirable to subdivide their periods of systole and diastole into shorter phases. In doing this, synchronous pressure curves recorded by optical manometers from the cardiac chambers and aorta, together with ventricular volume curves, are of great assistance.

While it would be tedious to describe, even superficially, the apparatus and technic required for recording pressure and volume changes accurately, the principles of such apparatus can be outlined in a few words.

Suppose (Fig. 1) that small chambers, A, B and C, filled with fluid and covered by very tensely drawn rubber membranes, are inserted through the auricular and ventricular walls and into the aorta. Each membrane will then respond to every pressure variation by a microscopic movement. This can be magnified and rendered visible by reflecting a narrow band of light from a small mirror fastened to the rubber. By allowing these beams to focus on a film (D) moving in a specially constructed camera, a true picture of the pressure variations can be recorded.

In order to record the volume changes of the ventricles, they are slipped as far as their a-v junctions into a glass oncometer covered by a rubber diaphragm in which an opening, corresponding in shape and size to the a-v ring, has been cut. This oncometer is connected

3. Wiggers: Am. J. Physiol. **42**:133, 1916; **40**:218, 1916.
4. Lewis, Feil and Stroud: Heart **7**:131, 1920.

with a large recording tambour. When blood is expelled and the ventricular volume decreases, the volume of air in the tambour is reduced by a corresponding amount, and the tambour lever falls. When the volume of the ventricles, on the other hand, increases as blood flows in during diastole, the lever rises. By connecting the interior of the large tambour with an optical segment capsule, the very slight pressure variations which correspond to the volume changes may be projected and recorded optically (Henderson [5]; Wiggers [6]).

While the conformation of such volume and pressure curves alters under different experimental conditions and varies also in different

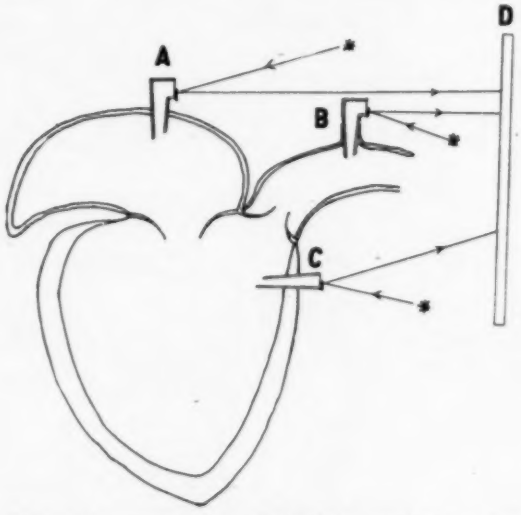

Fig. 1.—Schematic representation of principles employed to record pressure curves optically from auricles (A), ventricles (C) and aorta (B). D, sensitive photographic surface. Description in text.

animals examined, their general character and the time relations are represented fairly well by the curves shown in Figure 2. A careful study of many kilometers of such records obtained from over 200 dogs under a large variety of experimental conditions, together with a careful consideration of similar dynamic studies carried out by Garten,[1] Piper, Straub [7] and C. Tigerstedt, have led me to interpret and subdivide the ventricular cycle as follows: At the onset of ventricular systole (Fig. 2, I) the pressures within the auricle and ventricle are

5. Henderson and Collaborators: Am. J. Physiol. **16**:325, 1906; **23**:345, 1909.
6. Wiggers: Circulation in Health and Disease, 1915, Phil., Lea & Febiger.
7. Straub: Deutsch. Arch. f. klin. Med. **115**:531, 1914; **116**:409, 1914.

approximately equal. At this time, as indicated by the experiments of Dean,[8] the a-v valves are in the act of floating into apposition. As Henderson and Johnson [9] suggest, this movement probably is initiated by the sudden cessation of the jet when the peak of the presystolic auricular wave is reached. The first elevation of intraventricular pressure firmly closes these valves, and the ventricle then contracts in an absolutely isometric fashion. This first phase of ventricular systole,

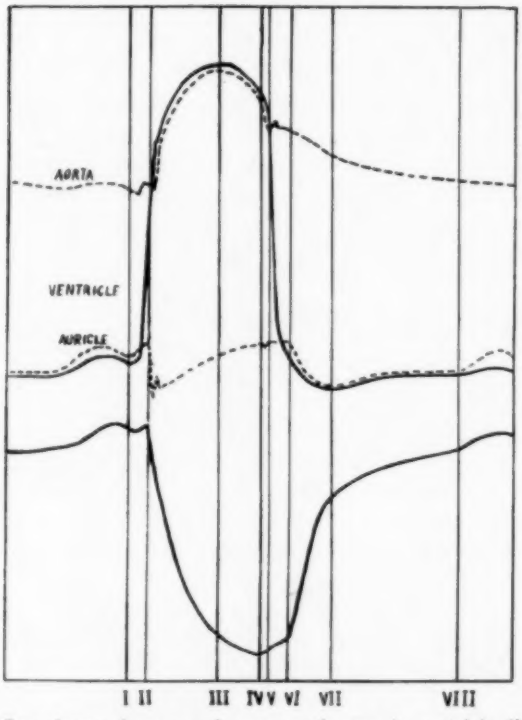

Fig. 2.—Superimposed curves of pressure changes in ventricle (heavy line), aorta (upper dotted line), and auricle (lower dotted line) together with volume changes in two ventricles (lower solid line). I-IV, systole; IV-VIII, diastole Detailed phases of each discussed in text.

extending from the beginning of the pressure rise (I) until the opening of the semilunar valves (II), is preferably designated as the isometric contraction phase.

As soon as intraventricular pressure exceeds intra-aortic pressure, the semilunar valves open and a comparatively large volume of blood

8. Dean: Am. J. Physiol. **40**:206, 1916.
9. Henderson and Johnson: Heart **4**:69, 1912.

per unit time is ejected. As long as the volume ejected remains greater than the outflow from the peripheral arterioles, the aortic and intraventricular pressures continue to rise. This summit (III) marks the end of a second phase of systole which I have designated as the maximum ejection phase. As soon, however, as the volume of the systolic discharge decreases to such an extent that it no longer equals the peripheral outflow, the aortic and intraventricular pressures begin to decline. This third phase (extending to IV) may be designated as a phase of reduced ejection. It terminates the period of systole.

At the onset of ventricular relaxation, aorta and ventricle are still in communication. The first event, viz., the approximation of the semilunar valves, is signaled by a sharp drop in both aortic and intraventricular pressures (IV-V), designated as the incisura. This marks a fourth or protodiastolic phase of the ventricular cycle. Following the closure of the semilunar valves (interpreted as taking place at V) and until the a-v valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity. This phase (extending from V to VI) may be designated as the isometric relaxation phase. With the opening of the a-v valves (VI), a rapid ventricular inflow begins. This continues until an equalization of pressure between the auricle and ventricle has taken place (VII), or until a subsepuent systole interrupts the filling. This is the sixth phase, which may be designated as the early diastolic inflow phase. In long cycles, and when auricular pressure is normal, a period of reduced filling or approximate stasis is indicated in the volume curve (VII and after), which may be designated, after Henderson's suggestion, as the phase of diastasis. Finally, there may be added an eighth phase during which the dynamic interval of auricular systole (VIII) affects the filling or pressure of the ventricles. This summary of the dynamic events occurring during ventricular systole and diastole and the suggested subdivision of the periods of systole and diastole into shorter phases is schematically indicated in Figure 3. On the diagrams are also indicated the average duration of these consecutive phases recently found in animals in which the thorax remained intact.

II. THE LAWS GOVERNING CARDIAC BEHAVIOR UNDER NORMAL AND ABNORMAL CONDITIONS

Under a variety of physiologic, pharmacodynamic and pathologic conditions, the heart must adapt itself to an altered venous return and changes in arterial resistance. In association with or quite independent of these, changes in rate and rhythm may take place. Again, the inherent functions of cardiac irritability and contractibility may be stimulated or depressed.

When such a combination of influences unite to modify the cardiac mechanisms, it may become quite perplexing, if not hopeless, to analyze the factors responsible for the resulting cardiac behavior. It is quite probable that this accounts for the facts (1) that "clinical hearts" do not always seem to conform to the laws and reactions established by laboratory experiments, and (2) that they do not always react to drugs as do the hearts of experimental animals.

It is important, therefore, that the laboratory investigations concern themselves primarily with the alteration produced in cardiac behavior when, as nearly as possible, only one of these variable influences operates at a time. The history of such researches has been the history of all investigations involving the use of complicated apparatus to

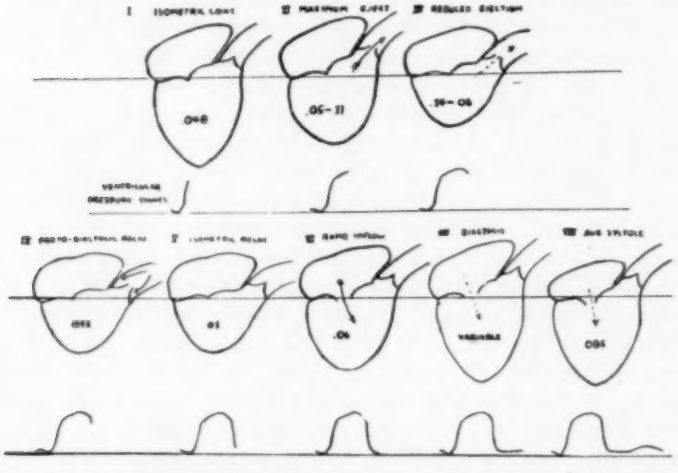

Fig. 3.—Series of pictorials illustrating the consecutive phases of the cardiac cycle established from pressure and volume curves. The extent of the ventricular pressure variations that have been completed at the end of each phase are also indicated. Upper series, phases of systole; lower series, phases of diastole.

unravel the mysteries of complex functions. One investigator demonstrates a series of striking facts; their uniformity suggests that they are grounded on a common factor or principle; a theory or law of cardiac behavior is formulated. Another investigator discovers certain facts which it is difficult or quite impossible to harmonize with such a conception. The older law is apt to be considered disproven and a new one is formulated. Rebuttal and counterchanges supported by new and still newer experimental facts fill many pages of scientific literature until he who follows every development cannot always decide what to believe either in his own work or in the experiments of others.

With the many differences of opinion regarding the fundamental laws controlling the functions of the heart beat, it is possible to keep from falling into this hopeless mental state only by bearing in mind that the disapproval of certain interpretations does not necessitate the discard of all experimental facts arrayed in its support. On the other hand, an investigator may have established a broad principle and yet have failed to realize the limitation of its applicability. We must admit, I believe, that while each new series of experiments has contributed its building stone, there still remains to be hewn out of unknown facts the keystone to that group of laws which regulates the heart beat under diverse conditions of circulation.

The Heart Rate as a Factor in Controlling Cardiac Efficiency and the Law of Uniformity of Behavior.—In a large series of experiments, Henderson and his co-workers [5] have contributed greatly to our understanding of the cardiac mechanism. They have demonstrated by experiments, that to me seem not to be negatived by apparently contradictory results of other investigators, that the ventricular filling occurs chiefly during the earlier portion of diastole, and that, in slowly beating hearts, there exists a phase of diastasis during which a very gradual filling of the ventricle takes place. They have done much toward demonstrating that the blood volume received by the ventricle during diastole also determines the amount discharged during systole. They have analyzed how variations in ventricular tonus can modify both filling and systolic discharge. They have demonstrated how, as the heart accelerates and the cycle shortens, the succeeding diastolic filling is encroached on more and more until the diastolic inflow is abbreviated and systolic discharge is greatly affected. That this tendency of the systolic filling to be decreased as the heart accelerates is one of the fundamental compensatory mechanisms which prevents an excessive minute volume from being discharged during rapid heart action, cannot be questioned. Henderson and his collaborators maintain further, however, that both under normal conditions of venous return as well as during states of increased venous pressure, the systolic discharge cannot be further affected by the venous pressure change or volume of venous return, but hold that it is determined solely by the duration of the cardiac diastole. They found that the volume curves of the ventricles, at any heart rate, are practically superimposable on portions of a standard curve obtained during a slow beat. This led them to formulate the "law of uniformity of cardiac behavior," according to which the systolic volume discharged is entirely a function of heart rate as long as the venous pressure is at or above normal.

The strict operation of this law has been questioned by subsequent investigators because it does not appear to square with other experi-

mental evidence. In 1914, I [10] found that systolic and diastolic blood pressures in man vary, independently of heart rate, which was interpreted to indicate that the rate of ventricular filling in man must alter during normal inspiration and expiration. Henderson and Haggard [11] have subsequently attempted to nullify these experiments by showing that systolic and diastolic pressures, measured by the sphygmomanometer method in man, failed to increase when a person is tilted on a board from a horizontal to a head-down position—a procedure obviously increasing the venous return and auricular pressure. Such experiments cannot be regarded as crucial, however, for, even if it admitted that the ordinary methods of estimating human blood pressure are sufficiently delicate to detect small variations, the fact that their experiments were always attended by heart rate changes, make it quite impossible to lend much significance to the pulse pressure change that occurred. On the basis of subsequent work, I am quite ready to admit, however, that my interpretation of pulse pressure changes during inspiration and expiration are more probably explained by a direct effect of the changing negative pressure on the aorta itself.

The view that the systolic discharge is unable to vary independently of heart rate when venous pressure is increased has been disputed by the results of Krogh,[12] Plesh [13] and Zuntz,[14] for it is difficult to explain the greatly augmented blood flow through the lungs during exercise in any other way than by assuming that the systolic discharge increases above normal even when the heart is very rapid. Krogh endeavored to show, furthermore, that such results may be harmonized with Henderson's volume curves if one of two assumptions is made, namely, either that the venous supply is normally inadequate, or that some myocardial factor increases the vigor of systole. Henderson and Barringer [15] again investigated the question as to whetеher the accelerator nerves can affect the amplitude of sytolic discharge independent of rate —with negative results. Subsequently, Starling and his collaborators [16] re-investigated the subject by means of their "heart-lung preparation" and concluded that the ventricular volume curves are not superimposable. Their volume curves indicated to them that when venous pres-

10. Wiggers: J. Exper. M., **19**:1, 1914.
11. Henderson and Haggard: J. Pharmacol. & Exper. Therap. **11**:189, 1918.
12. Krogh: Skand. Arch. Physiol. **27**:126, 1912.
13. Plesch: Centralbl. f. Physiol. **26**:90, 1912.
14. Zuntz: Ztschr. f. klin. med. **74**:347, 1912.
15. Henderson and Barringer: Am. J. Physiol. **31**:228, 352, 1913.
16. Starling and Collaborators: J. Physiol. **44**:206, 1912; **47**:275, 286, 1913; 348, 357, 465, 1914.

sure increases above normal, the systolic stroke is greatly increased without any change in heart rate. Similar conclusions have also been reached by Straug [7] and Socin.[17]

We may inquire what changes must necessarily take place if the systolic discharge increases at the same time that the heart accelerates. Obviously, such a condition is made possible only by an increase in the expulsion rate or by a lengthening of the ejection phase. Recent experiments in which I measured the duration of systole after saline infusion indicate that this causes a definite prolongation of the ejection phase, quite independent of diastole length.

On the basis of recent experimental work, Katz and I [18] have found it necessary to conclude also that, even under quite normal conditions, the systolic discharge of the heart may not be regulated by changes in the duration of cycle alone. Our evidence is based on the following considerations: Although emphasis has not been laid specifically on the fact by Henderson and his co-workers, it is evidently a corollary of the "uniformity of behavior law" that the duration of systole is fixedly related to cycle lengths under all conditions which normally produce a change in heart rate. As the cycle shortens from a very long to a very short cycle, the phase of systolic ejection must, at first, be very little affected but becomes progressively shorter. By determining the theoretic systole and cycle lengths and expressing this as a systole: sycle ratio, it was found possible to construct a curve of theoretical s/c ratios. To this curve, the actual s/c ratios at different heart rates should conform if the law of superimposability holds good. It was found, however, that, while the actual s/c ratios obtained during normal rates and during vagus beats coincided reasonably well, the ratios were very much below this curve when the heart rate increased during stimulation of the accelerator nerve.

In carrying this work still further, Katz and I, working independently and by different methods, have obtained other evidence which indicates that during vagus slowing the periods of systole and diastole are also not strictly related to the length of previous diastole. When, for example, the peripheral end of a vagus nerve is stimulated with a current producing moderate slowing, systole increases in length for several succeeding beats, becoming stationary only when a new equilibrium has been established. This occurs regardless of previous diastole lengths and often contrary to them. After reflex slowing induced by central vagus stimulation, the duration of systole in a few experiments was longer than in peripheral vagus stimulation, even though a much greater slowing was produced by previous peripheral stimulation.

17. Socin: Arch. f. d. ges Physiol. **160**:132, 1914.
18. Wiggers and Katz: Am. J. Physiol. **53**:49, 1920.

When partial asphyxia produces cardiac slowing, the periods of systole may remain unchanged or even become abbreviated.

Such results indicate that while a constant relation between systole and diastole lengths, such as complete superimposability of beats demands, approximately obtains when a stable equilibrium has once been produced after direct vagus stimulation, there are other factors at work which more than counterbalance such a control of systole length.

On the basis of all these investigations, we must conclude that, while the systolic discharge is mechanically determined by the heart rate when other factors are unchanged, the simultaneous variations of these factors even under normal conditions prevent the beats from being superimposable.

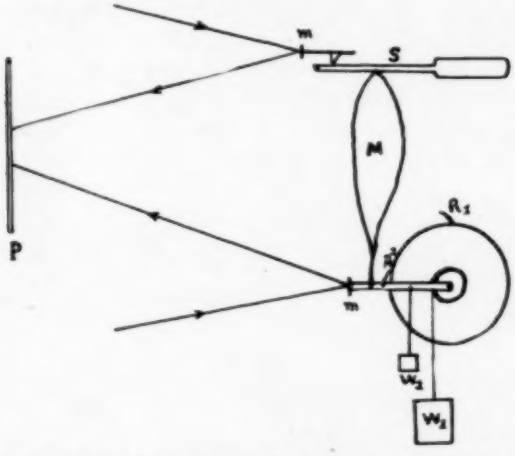

Fig. 4.—Diagram showing arrangement of muscle activating a work adder, with attachments for photographically recording tension changes and length changes, optically. S, spring; m, small mirrors reflecting light beam to photographic film; P. Further description in text.

The Response of the Heart to Changes in Venous Return and Arterial Resistance.—The response of the normal heart to changes in venous return and alterations in arterial resistance have been studied by recording both the volume curves of the two ventricles, and the pressure curves from the separate ventricles. While such methods have their difficulties and drawbacks, their use has served to advance our understanding of an important phase of cardiodynamics. In order to grasp the significance of such investigations in their fullest, however, it is necessary to recall the nature of the contraction processes in a skeletal muscle which operates in a manner similar to the heart.

It has been pointed out by Henderson that, with certain reservations, the heart contracts as a skeletal muscle operating a work-adder. In such an arrangement (Fig. 4) the weight (W_1) which the muscle is required to lift is supported by the ratchet (R_1,) and, consequently, weights the muscle only during contraction. During the rest period, as well as during the process of relaxation, the muscle is stretched by a smaller weight W_2. Obviously, the greater this weight becomes, the greater the length of the resting muscle. This resting length of the muscle is referred to as its initial length. . When this weight increases, the muscle fibers are not only lengthened more but are also placed under a greater tension, referred to as its initial tension. Changes in this initial tension may be recorded graphically and evaluated by attaching the upper end of the muscle to a stiff spring, the very slight movements of which can be greatly magnified and projected (Fig. 4). A muscle so arranged is said to be "after-loaded." Before it can shorten its tension must be increased sufficiently to overcome the load W_1, i. e., it first contracts isometrically. Such a tension variation will be recorded by the upper lever a short interval before the lower lever begins to register a decrease in length. This accomplished, the ratchet R_2 engages and the weight is raised during the remainder of the contraction phase. Inasmuch as the tension during this phase of contraction does not alter appreciably, it is said to contract in an isotonic manner. At the onset of relaxation, the ratchet lever R_1 engages and the relaxation process is assisted by the small weight W_2.

In the normally beating heart, the venous pressure represents the distending load (W_2) and determines the initial tension as well as the initial length of the ventricular muscle fibers, while the arterial pressure corresponds to the lifted load (W_1). It is clear, therefore, that changes in initial tension as well as the tension changes during contraction and relaxation may be conveniently followed by recording optically the intraventricular pressures. Changes in the length of the muscle fibers, as Frank, Paterson, Piper and Starling and others have pointed out, may be evaluated most satisfactorily by studying the changes in the ventricular volume during consecutive phases of the heart cycle.

In 1914, I reported [6] experiments which seemed to demonstrate that every increase or decrease in the volume of blood returning to the right auricle affects simultaneously the initial tension, height, and contour of the right intraventricular curve. These experiments were the first to demonstrate that the laws derived by Frank from a study of the frog's heart apply also to the naturally contracting mammalian ventricle. In brief, the conclusion seemed justified that *the gradient of the isometric pressure rise as well as the systolic pressure-maximum are determined by the initial tension* as long as marked changes in

arterial resistance or alterations in the inherent contractility of the heart are not produced. At the same time, it was shown that any increase in pulmonary arterial resistance is also capable of altering the pressure-maximum in the right ventricle under conditions of unchanged venous inflow. Finally, it was pointed out that independent of, or coincident with, these factors the pressure-maximum may be determined by the inherent contractility or irritability of the heart itself.

Shortly after the publication of this work, a series of investigations were published which apparently analyzed the reactions of the heart to increased venous return and increased arterial resistance in a much more fundamental manner. This was accomplished by limiting the circulation to the heart and lungs and controlling independently the venous inflow and the arterial resistance. With such a "heart-lung" preparation dynamic experiments were carried out in London, by Starling,[16] working at various times in association with Knowlton, Mark-

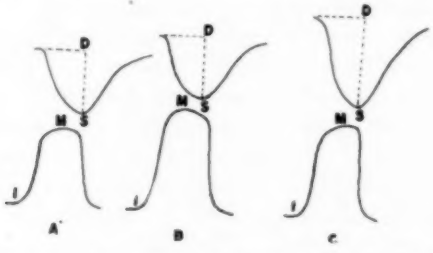

Fig. 5.—Diagrammatic representation of ventricular volumes (upper curves) and pressure changes in left ventricle (lower curves), according to results of Patterson, Piper and Starling. D, diastolic volume; S, systolic volume; D-S, systolic discharge; I, initial pressure; M, pressure-maximum. A, normal controls; B, after increased arterial resistance—initial pressure (I) unchanged, initial volume (D) increased, pressure-maximum (M) higher, systolic discharge (D-S) unaltered. C, after increased venous inflow—initial pressure (I) decreased, initial diastolic volume (D) increased, systolic discharge (D-S) and pressure-maximum (M) increased.

walder, Patterson and Piper, and contemporaneously by Straub[7] in Munich. Subsequently, Gesell[19] in this country, has also utilized a similar method of experimentation.

The first investigations of Starling and his associates showed that the systolic discharge of the ventricle at any constant rate is unaltered by very considerable change in arterial resistance as long as the inflow is kept constant. On the other hand, they found that, within wide limits, the heart is able to increase its output in direct proportion to the venous inflow. Similar results were obtained by Socin[7] and de Heer.[20]

19. Gesell: Am. J. Physiol. **39**:239, 1916; **40**:267, 1916.
20. de Heer: Arch. f. d. ges. Physiol. **148**:45, 1912.

In studying the cardiac reactions more in detail, Patterson, Piper and Starling obtained results which are diagrammatically illustrated in Figure 5. Their records show that when the venous inflow increases, the ventricles are more distended in diastole and the systolic discharge increases (Fig. 5, A and C). The initial tension in the left ventricle, however, may not increase, but, on the contrary, may actually be lower. Nevertheless, the intraventricular pressure-maximum appears to rise.

When arterial resistance alone was raised, they again found an increased diastolic volume due to a retention of blood during the first few beats. Their tracing indicates that once dilated to a stable capacity, the heart expels at least as large a systolic volume as before the increase in resistance (Fig. 5, A, B). In studying the intraventricular pressure changes accompanying such reactions, it was also found that the left intraventricular pressure-maximum increases, that the pressure

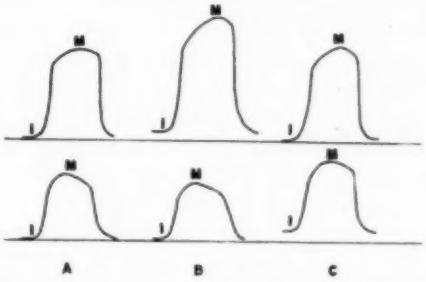

Fig. 6.—Diagrammatic representation of pressure changes in right (lower) and left (upper) ventricles according to Straub's results. A, normal control curves; B, after increased arterial resistance—initial pressure (I) increased in left ventricle, unaltered in right, pressure-maximum (M) higher in left ventricle, lower in the right. C, after increased venous inflow—initial pressure (I) increased in right but not in left ventricle, pressure-maximum (M) increased markedly in right and very slightly in left ventricle.

gradient rises steeper and that the duration of the period of systole is increased. In some cases, however, the noteworthy observation was made that the initial tension is scarcely affected in the left ventricle. These results, together with observations on the isometric contraction curves obtained from the terrapin heart, led them to conclude that, "in the reaction of the heart to increased venous inflow and increased resistance, the only factor which constantly varies with the response of the ventricles is the volume of the heart, i. e., the length of its muscle fibers." They believe, on the basis of such experiments, that we are justified in ascribing the increased energy of the cardiac contractions under conditions of increased inflow or augmented resistance entirely

to alterations in the length of the muscle fibers and not to change in tension on the fibers, which, as they interpret it, may or may not be present at the same time.

The contemporaneous experiments of Straub [7] led on the whole to similar, yet in some vital respects, different conclusions. He also found that, under a constant venous inflow, increased arterial resistance leads to a systolic retention resulting both in systolic and diastolic distention. The systolic discharge remained unaffected. His optical pressure curves indicated, moreover, that, in the left ventricle, not only the maximum pressure, but also, the initial pressure increases (Fig. 6, cf A and B). Such results, contrary to those reported by Starling and his co-workers, would indicate that an increased pressure-maximum is constantly associated with, if not fundamentally due to, an increased initial pressure. In the right ventricle, however, he found no increase in height nor elevation of the initial tension; in fact, in some cases, the pressure-maximum seemed to be reduced. These results, it will be recalled, are quite contrary to those previously reported by Führer and Starling [16] who found that a "backing up" of blood always occurs when the left heart works against an increased resistance. In attempting to harmonize these discrepancies, Straub pointed out that he also was able to obtain such "back pressure" effects when the arterial pressure at the start was low and the coronary supply therefore insufficient to maintain the heart in prime condition. Straub considered the latter reaction as one of a hypodynamic and uncompensating heart; Führer and Starling considered it the reaction of a normal heart. We shall revert to a discussion of this question later. When the inflow rate was increased but the arterial resistance kept constant, Straub found, similar to Starling and his co-workers, that the two ventricles dilate somewhat and expel larger systolic volumes. The intraventricular pressure curves taken from the two ventricles again showed differences (Fig. 6, A and C). In the right ventricle, changes similar to those reported by myself were constantly observed, i. e., increased diastolic filling always occasions an increased initial tension and a higher pressure-maximum. In the left ventricle and in confirmation of Starling's results, no changes in initial tension occur although the pressure curves did become somewhat higher. According to these results, the increased discharge of the right ventricle is unable to affect the diastolic filling of the left sufficiently to cause an elevation of initial tension. While Straub interprets his results as indicating that initial tension is the primary factor in determining ventricular efficiency, the increased systolic discharge of the left ventricle must, in such cases, be assigned to changes in initial length or initial volume rather than initial tension.

In investigating the importance of auricular systole in the dynamics of the ventricle, Gesell,[19] was compelled to consider the broader question as to whether initial length or initial tension primarily determine ventricular efficiency. In the auricle of the river turtle, which shows rhythmic fluctuations in tonus, he found it possible to study the effect of changes in tension and length independently. His results indicated that in the auricle of the turtle, increased strength of contraction may accompany either increased length of fiber while initial tension remains constant, or increased tension while initial length remains the same. Further experiments on a mammaliam heart-lung preparation led him to conclude that this also applies to the mammalian ventricles. The latter experiments may not be regarded as quite conclusive, however, because the method employed to record variations in tension and length do not appear to be quite adequate for the study of the mammalian circulation. As a result of his work, Gesell suggests that, while both initial length and initial tension may determine ventricular efficiency, the surface-volume relations are also concerned.

With these conflicting views before us it seems desirable to re-investigate whether measurable differences of initial tension fail to accompany such experimental procedures as have been definitely shown to increase initial volume. This, I have recently attempted in intact animals. At once we may anticipate the loud objections that experiments carried out on intact animals can, of course, not prove valid either the one contention or the other.

Extensive experience has convinced me that it is not so difficult to control or evaluate the separate factors in intact circulation experiments as has been claimed. If the vagi nerves have previously been severed, variations in heart rate are no more extensive than those which occur in perfused hearts. The venous return may readily be reduced by compression of the vena cava and increased by the injection of innocuous normal saline. In neither event is arterial resistance altered appreciably. Increased resistance may be induced either peripherally by vasoconstriction or more centrally by mechanical compression of the aorta. If carried out for intervals which are short but quite long enough to obtain observations, the venous return is either not sufficiently affected or, if modified, can be evaluated in interpreting the reactions.

Are the experimental conditions in the heart-lung preparation better or more controllable? The very fact for which these experiments are lauded, viz., that each factor—venous inflow, arterial resistance and rate—may be controlled at will, makes them a source of trouble. In such schemes, it is the first duty of the experimenter so to adjust the artificial factors (the controllable factors) that the heart beats after a fashion which he interprets as normal. What criterion other than instinct can

guide him? We have already pointed out that the adjustment of the artificial resistance to the inflow volume apparently determines whether or not a "back pressure" effect takes place on raising the arterial resistance. Each experimenter will be ready to admit that his adjustment approximates normal. Führer and Starling find "back pressure effects" as far back as the right auricle on increasing artificial resistance; Straub finds that the pressure in the right ventricle decreases. Both results can not apply to the intact normal circulation. Who shall judge between them? I have been able to show in similar heart preparations that, with constant arterial resistance, an increased systolic discharge may cause either an increased or decreased pulse pressure in the arteries, depending on whether the arterial resistance during the so-called "normal" is relatively great or small, as compared with the venous inflow. Both reactions cannot be characteristic of the intact circulation. The fact that mean arterial pressure approximates the normal found in animals of course means nothing whatsoever. In short, I believe that in many instances it is possible to set the "normal" so that absolutely diverse propositions may be clearly (!) demonstrated with equal facility.

Aside from the judgment of the experimenter, we have possible alterations in the physiological condition of the perfused heart to deal with. Does it react as the heart in the intact circulation? Always, it is separated from all nerve control—not without its effects on the duration and strength of ventricular contraction. Usually, also, the pericardium is opened—causing, as has been shown in Starling's own laboratory by Kuno, important changes in the distention of the ventricles. Commonly also, the capacity of the rubber tube substituted for the aorta is too small to accommodate, in a natural manner, the ejected blood, so that the entire systolic volume must each time be forced through a small cannula tied into the narrow lumen of the innominate artery. In the heart-lung preparation, the blood supply of the heart also changes in a manner which is quite abnormal, whenever the resistance increases. If the aortic resistance increases in the natural circulation, short circuits are always available through which an excess of blood may flow. In the heart-lung preparation the only short circuit is the coronary system which then apparently allows exorbitant volumes of fluid to flow through it. A few direct observations may be interesting: If we use the figures of Patterson, Piper and Starling, we can only conclude that normally from 25 to 35 per cent. of the entire systolic discharge passes through the coronary system, a volume which if correct represents a most abnormal state of the coronary circulation which certainly does not conform to the intact heart. Straub found that after compression of the aorta, the coronary blood flow increases

so greatly that right auricular pressure is thereby augmented—a condition just the reverse of that obtaining in the intact circulation. Frequently also, the heart is supplied with a blood-saline mixture of unnatural composition. In Straub's experiments, for example, the deficiency of carbon dioxid in the blood, according to his own interpretation, caused the hearts to beat at the excessive rate of 300 per minute. Finally, it seems very doubtful whether the preparation accomplishes the task for which it is specifically employed. I question, for example, whether it is possible to alter any one factor—e. g.,—heart rate, venous pressure or arterial resistance—without at the same time affecting some other factor. Thus, it appears both from the records of Patterson, Piper and Starling and those of Straub that, whenever the arterial resistance increases considerably, the filling pressure in the right auricle also augments. Again, I have found it exceedingly difficult in similar experiments to dissociate changes in temperature from changes in venous inflow; the two seem intimately interdependent. Whenever the inflow rate is increased, a tendency exists to increase the temperature of the heart muscle; when it is reduced, the reverse tendency exists. The temperature change may be only 0.5 C.; but what changes in inherent irritability and contractibility may not this induce! How can the influence of this factor be separated from that produced by augmented inflow itself? On the whole, who dares to say that the heart in such preparations reacts as would an intact heart or that every factor can be perfectly controlled?

I cite these objections not to condemn the method, nor to discourage its employment in the analysis of the cardiac mechanisms. On the contrary, I am of the opinion that its employment has greatly enhanced our knowledge of the fundamental laws according to which the heart *can* react. I merely wish to emphasize the possibility that such laws may apply only to special conditions and must always be transferred to the intact circulation with the greatest reserve and caution.

With such reflections in mind, I have recently investigated the ventricular pressure and volume changes during conditions of altered arterial resistance and venous inflow on intact animals, for, in such experiments, in contrast to studies on the heart-lung preparation, it is possible to study what probably *does* happen when the heart reacts to different influences. Both right and left intraventricular pressures were simultaneously recorded by optical manometers. In some experiments the volume changes were also recorded; in others, volume curves were omitted in order to test the same procedures in animals in which the natural pericardial support of the ventricles was maintained.

In seventeen experiments, so far completed, it was found, without exception, that any sudden increase in venous return which increases

also the volumes of the ventricles, always promptly elevates the initial tension and pressure-maximum in the right as well as left ventricle. This is illustrated by the records shown in Figure 7, II. Curves "1" are normal controls. Fifty c.c. of warm saline solution was then allowed to flow into the external jugular vein in twelve seconds. In

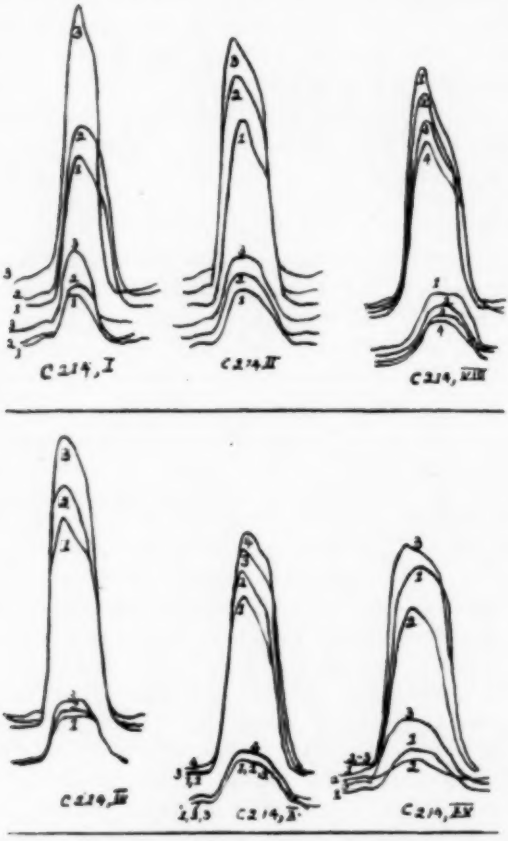

Fig. 7.—Superimposed tracings of right (lower) and left (upper) intraventricular pressure curves, after experiments of author. I, normal as compared with effects during asphyxia; II, normal as compared with saline infusion effects; VIII, normal as compared with decreased venous return after vena cava compression; IV, normal as compared with effects of vaso-constriction; X, as compared with effects of aortic compression; XV, normal as compared with effects of chloral (2) and strophanthin (3).

other experiments, this had been shown to definitely increase the diastolic volume of the ventricles and augment the systolic discharge in

from 2 to 3 seconds. Four seconds after, curves "2" were recorded. Both intraventricular pressure curves show an elevation of initial, as well as maximum pressure. Toward the end of the infusion, the third series of curves were taken; a further elevation of initial and maximum pressures in both ventricles is obvious.

Reduction of the venous inflow produced by clamping the inferior vena cava has precisely the reverse effects on initial and maximum pressure in the two ventricles. This is shown in records labeled as obseravtion VIII. Such changes in initial pressure occur with great promptness when the volume of fluid returned is either decreased or increased. Thus, in observation VIII, "1" shows the normal control, "2," "3" and "4" illustrate the changes taking place during the second, fourth or sixth beats after compression of the vena cava.

When arterial resistance increases either through intense vaso-constriction or mechanical compression of the aorta, the initial pressure is always elevated when it is of sufficient degree to cause a dilation of the ventricles. The details of these changes are illustrated in the series of records shown in IV and X. Observation IV indicates the final results during intense vaso constriction reflexly induced by stimutating the central end of a divided vagus nerve. Curves "1" are normal controls. While arterial pressure (recorded supplementary) was on the ascent, curves "2" were recorded. At the height of the pressure reaction, curves "3" were taken. In both, a considerable elevation of initial pressure is indicated in the left ventricle pressure curves and a relatively smaller increase is discernible in the right ventricle. In observation X are noted the immediate effects of raising the arterial resistance through mechanical compression of the thoracic aorta. Curves "1" are normal, curves "2" represent the pressure changes during the first beat following compression. The pressures in the right ventricle are unaffected. The pressure-maximum increased by virtue of the higher resistance and pressure existing during the contraction process. The initial pressure has not elevated. Curves "3" show the changes in the third beat after compression. Increased initial tension and pressure-maximum occur in the left ventricle, the pressure in the right still remaining unchanged. Curves "4" represent the fifth beat after compression. Initial pressure and pressure-maximum are further elevated in the left and, for the first time, in the right ventricle also.

Experiments of another order have also been carried out. In these, the ventricular volume curves were recorded on a slowly moving smoked paper; the two intraventricular pressure curves, as before, at the first indication of an increase in diastolic volume (initial length) after slow saline infusion, optical pressure curves were at once recorded.

Comparison with normal curves showed that the initial pressure increase in the right ventricle was never dissociated from an alteration in initial diastolic volume.

This state of affairs obviously holds good only as long as the inherent functions of the cardiac muscle are not excited or depressed. There are many evidences of deviations from this rule; both in the literature emanating from other laboratories and my own. Thus, when the initial pressure becomes elevated to an excessive degree, the intraventricular pressure-maximum no longer increases but becomes lower at the same time that the systolic discharge lessens. So also, when the heart is long distended by a great inflow or is required to react against a very high arterial resistance for a long time its subsequent power of response is reduced. The irritability of the heart may also be depressed or stimulated by chemical agents, in which case the pressure-maximum and systolic discharge are not related to the initial pressure. This is illustrated in observation XV, in which curves "1" again show normal controls. Curves "2" are representatives of pressure changes following the use of chloral hydrate. Initial pressure is greatly elevated in the right, very slightly in the left ventricle. In spite of this, the pressure-maximum is lower in both ventricles. The heart was obviously dilated. Neither increased initial pressure nor increased initial length determines the vigor of the ventricle when the myocardium is depressed. Curves "3" were obtained after subsequent use of strophanthin. The tension maximum increased above normal in both ventricles—the initial tension remaining unaltered in the left and decreased in the right.

Viewing all the experimental evidence in the light of the more fundamental work of Blix, Hill and others on skeletal muscle, we must be ready to admit that the dynamic efficiency of the ventricle may be fundamentally determined by such factors as initial length, and diastolic surface-volume relations. It is not so evident, however, (except, perhaps, under conditions of very small venous inflow, or where the ventricle has lost its tonus completely) how any increase in diastolic volume (and initial length) can take place otherwise than by the force of an increased initial tension. The ventricles are filled to capacity even under very low auricular pressures. It would seem that any additional increase in volume must necessitate a stretching of the elastic and tonic walls of the ventricle. This requires an increased auricular and increased initial pressure. The pressure required to stretch the walls sufficiently to admit a definite volume increase need not be great, if the tonus is low; but must be considerable, if it is high. The pressure increase is not proportional to the volume increase; but an increase must exist. We may reiterate: While initial length of

ventricular fibers and diastolic surface-volume relations may fundamentally determine myocardial efficiency, it is difficult to picture how these factors can be increased except through an increase in initial tension.

III. THE DYNAMICS OF THE CIRCULATION IN HEART DISEASE

The signs and symptoms arising from acute or chronic cardiac disease are the expressions of dynamic consequences which occur when the normal valvular mechanism is impaired or the functional capacity of the ventricular myocardium is affected. As the latter are always concerned more or less in valvular effects, it seems desirable to analyze, on the basis of experimental results, how the myocardium becomes abnormal in its function, to consider the factors of safety that are at once called into play, to analyze how additional compensatory mechanisms gradually develop, and finally, to attempt an answer as to why these mechanisms ultimately fail to accomplish the task for which they were developed.

The Hypodynamic or Inherently Weakened Heart.—Under this heading I mean to catalogue cardiac conditions in which the working capacity of the ventricles has been reduced. It is, I believe, the condition which so frequently follows or terminates severe febrile or infectious processes. Clinically, it is recognized chiefly by the feeble heart sounds (particularly the first) and the small pulse amplitude. The latter has definitely been proven to be caused by the decreased systolic discharge; the enfeeblement of the first sound I [21] have recently shown to be related to and diagnostic of a reduction in intraventricular tension.

It is probable, therefore, that we have, in this hypodynamic heart of the clinic, a condition not unlike that produced by depressant drugs such as chloral, chloroform, etc., and consequently, we may venture an interpretation of the cardiodynamics on the basis of experimental results obtained from the use of such drugs.

The capacity of the ventricle for work is, of course, a function both of pressure and volume, as well as time. O. Frank has expressed it by the integral, $A = \int_{T_0}^{T_1} P.\ V.\ dx$ in which A represents the work; P, pressure; V, volume; T_0, time of opening of semilunar valves; T_1, the time of closure of the semilunars. Owing to the facts that the volume curves of each ventricle cannot be separately recorded and that initial tension is a function both of aortic resistance and venous filling, it has not been found possible to apply this formula in estimating the working capacity of the mammalian heart beating under different

21. Wiggers: Arch. Int. Med. **24**:471, Sept., 1919.

conditions. A separate study of the changes in the volume and pressure curves of the ventricles has given us, however, a clue to the essential changes taking place in the hypodynamic heart. Socin,[17] who studied the volume changes, systolic discharge and minute volume of the heart depressed by chloroform, found that such depression expresses itself primarily by a decreased systolic discharge and, in consequence of the inefficient discharge, by a dilation. The depressed heart retains only to a lesser degree its power of responding to changes in venous inflow or arterial resistance. If, for example, the arterial resistance is increased, the systolic discharge is not maintained as in the normal heart but continues reduced for a long time. This leads to dilation. Again, when the venous pressure is increased, it does not respond with an increased output as the normal heart, but the discharge remains unaffected.

Similar evidences of its inability to respond to increased requirements are shown by studies of the pressure curves. Experiments, not yet completed but well under way, point to the conclusion that, when the heart is acutely depressed by such agents as chloroform, chloral, alcohol, etc., the intraventricular pressure progressively rises less abruptly and to a lower level in spite of the fact that the initial pressure is elevated and the diastolic ventricular volume, to judge from volume curves, is actually greater.

The heart gradually recovers from such effects. This, we are accustomed to attribute to the fact that the chemical action gradually wears off. Pressure curves indicate, however, that this "wearing off" effect is not entirely due to the cessation of a toxic action but involves rather a process of compensation. This seems to occur as follows: As a small quantity of blood is retained during successive systoles, the initial tension and initial distention of the ventricles is greater. When this has gone sufficiently far, the hypodynamic heart reacts to the higher initial tension and the amplitude of the pressure curve again increases. In these depressed hearts, the impression is clearly gained that initial tension fundamentally determines the pressure relations; and present one instance as to why the analysis of the relative importance of initial length, and initial tension, in determining cardiac efficiency is of more than academic interest.

If cardiac depression is more severe, the ventricular pressure is not elevated to normal even if the initial pressure itself is considerably higher. By virtue of the higher initial pressure, the ventricle dilates more and more and the pressures in the left auricle and entire pulmonary circulation have a tendency to become elevated. Marked pulmonary congestion is probably avoided because the output of the

depressed right ventricle is diminished by an amount nearly equal to that of the left. Stagnation of blood in the veins and liver without pulmonary congestion can thus be explained in a logical manner.

If the influences depressing the contractile power of the ventricles are removed, or if they are neutralized by suitable cardiac stimulation, gradual recovery may take place. Such experiments favor the use of such stimulating drugs as digitalis and strophanthin in purely myocardial types of depression.

Cardiac Strain and Fatigue.—Cardiac strain begins when the normal or hypodynamic heart is required to eject its blood against a greater arterial resistance, or, what amounts to the same thing, a higher diastolic pressure. The reactions correspond to those previously analyzed when the arterial resistance is increased experimentally. As a result of the greater load, a small increment of blood remains behind, at once distending the ventricle. As long as the elastic and tonic resistance of the myocardium is not impaired, however, it at once elevates the initial tension. This safety mechanism causes a larger pressure elevation and a restoration of the discharge to normal. The earlier phases of this reaction are undoubtedly beneficial. With the higher pressure developed during the isometric phase goes an intensification of the first sound; and with the closure of the semilunar valves at a higher diastolic level, we get, as has been experimentally demonstrated, an accentuated second sound. As long, therefore, as both sounds remain intensified, the heart is responding by adequate safety mechanisms.

If the factors increasing diastolic pressure operate too rapidly, or if the elevation is continued too long, a second phase of cardiac strain develops. During this stage, as Bruns [22] has shown in the frog's heart, the inherent contractility suffers. In the mammalian hearts, the intraventricular pressure curves do not mount so high and the isometric slope becomes more gradual, even though there is a progressive dilatation of the ventricle and an increased initial pressure. When this occurs, the second sounds may remain intensified, while the first sound vibrations become reduced in amplitude. Since the tonic contraction of the cardiac muscle and its elastic resistance is unable for long periods of time to resist the gradually increasing strain, the heart begins to weaken and finally gives way (Bruns). The ventricle then dilates enormously. This marks the onset of cardiac fatigue. Straub's experiments indicate that when this occurs the pressures in the left auricle become greatly elevated and the lungs markedly distended. The right ventricle, in consequence, is compelled to contract against a greater load; it then passes through the same phases of cardiac strain as the left. During the time that dilation of the left ventricle is backing blood into the pul-

22. Bruns: Deutsch. Arch. f. klin. Med. **113**:179, 1913.

monary circuit, the efficiently contracting right ventricle adds normal volumes of blood to the pulmonary side, consequently, pulmonary congestion cannot fail to supervene during the second stage of cardiac strain, while there may be no evidence of venous congestion.

Either one of two sequels must follow: the right ventricle may pass to the stage of dilation causing the venous pressure to rise and pulmonary pressure to fall, or new compensatory mechanisms may come into play which help to reestablish normal relations.

Tonus and Dilatation.—These terms are constantly employed by physiologists and clinicians alike, without always a clear conception of what they really imply. When the exposed heart appears large and distended during diastole, we speak of a dilated heart or one having a low tonus. If, on the other hand, the diastolic volume is small, we are apt to speak of tonus as being high. As Patterson, Piper and Starling point out, the state of distention and tone are not necessarily related "for the volume may be merely determined by the amount of

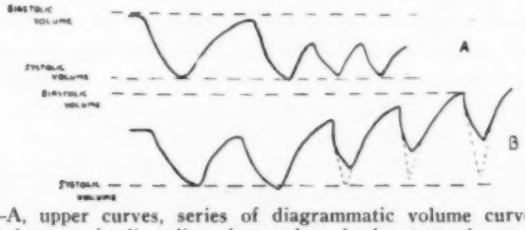

Fig. 8.—A, upper curves, series of diagrammatic volume curves showing mechanical decrease in diastolic volume when the heart accelerates, according to conceptions of Henderson. B, lower curve showing effect of increasing diastolic volume due to increased venous inflow when tonus remains normal (dotted lines) and when it is reduced (solid lines). Result, is a larger systolic volume in the former, and unaltered discharge in the latter instance.

blood entering from the veins." Henderson has shown that the diastolic volume of a heart distended by high venous inflow is necessarily greater than that of a heart which receives only a small venous inflow. Obviously, the diastolic volume of the heart is usually passively determined and in such cases the more dilated hearts are the more efficient; both because the initial and maximum intraventricular pressures are higher, and because the systolic discharge is greater (Fig. 8, A). For the sake of differentiating, let us speak of this as a physiologic dilatation (tonogenic dilatation of Moritz).

Clinically, the term "dilatation" is applied to a condition in which the heart is dilated during diastole while the systolic discharge is diminished; or, perhaps, more precisely stated, when the dilation is not accompanied by a larger discharge. In other words, the heart is dilated during systole as well as diastole; a relation that may be expressed by the

volume curves diagrammatically shown in Figure 8, B. Let us hereafter refer to this type as pathological dilatation (myogenic dilatation of Moritz).

Pathologic dilatation is frequently attributed to a failure of cardiac tonus; the physiologic type, to a passive distention in which tonus persists. According to such conceptions, Patterson, Piper and Starling consider the term tonus "as synonymous with the physiological condition or fitness of the muscle fibers and its measure is the energy set free per unit length of muscle fiber at each contraction of the heart." A heart with good tonus will carry on a large circulation and nearly empty itself at each contraction, a heart with defective tonus can eject the same systolic volumes, only when its fibers are lengthened (Fig. 8, B). This is also essentially the conception formulated by Moritz.[23]

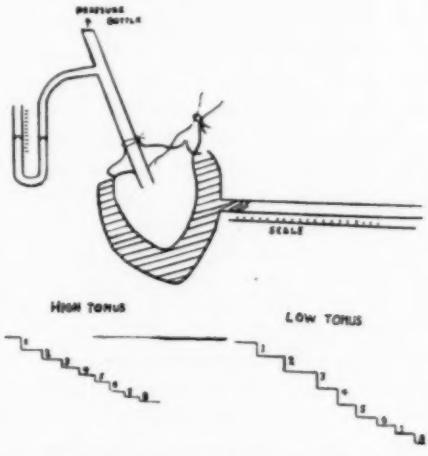

Fig. 9.—Diagram illustrating principle of measuring volume—elasticity coefficient of relaxed ventricles. Lower curves illustrate distention curves in heart with high and low tonus, each step representing an equal increment of intraventricular pressure.

While this expresses the end effects of tonus changes, and relates the importance of tonus to cardiac efficiency very well, it does not clearly define the nature of tonus itself, nor does it analyze the mechanisms through which tonus governs cardiac efficiency. To the physiologist, the term "tonus" has come to signify a sort of a sustained partial contraction of muscle tissue by virtue of which the muscle fibers resist stretching more than they would by virtue of the inherent elasticity

23. Moritz: Deutsch. Arch. f. klin. Med. **66**:349, 1899.

alone. According to this conception, the ventricular tonus varies directly as the volume-elasticity coefficient of the relaxed heart, i. e., the ratio of the pressure increase to the volume increase, $\frac{\Delta p}{\Delta v}$.

This relation may be studied after the fashion schematically illustrated in Figure 9. Let us suppose that, in such a preparation, sufficient fluid is admitted into the ventricle to raise the intraventricular pressure by eight equal increments. The volume changes corresponding to each of, say eight, such pressure elevations may then be plotted in steplike fashion. Comparison of curves from ventricles under varying conditions of tonus make it quite obvious that when tonus is low, a much greater increase in volume accompanies a given pressure increase than when tonus is high; or, stated in the reverse, the same volume change is associated with a much greater pressure change when tonus is high than when it is low.

We may now again examine into the reasons why a heart with deficient tonus is less effective than the normal. Two hearts, distended to equal volumes, would have equal initial lengths. If this is the dominant or only factor determining the power of the heart to respond, we can only assign the decreased working capacity to an impairment of the muscular irritability itself. Such is apparently the conception of Starling and his associates. If, however, initial tension is primarily concerned in determinig the working capacity of the heart, then the reduced working capacity of the ventricle during atonia may be accounted for by the fact that, at equivalent initial volumes, the initial pressure is lower in the atonic than in the normal heart.

The factors which may modify cardiac tonus have not all been definitely established on an experimental basis. Thus, from the experiments of Socin,[17] it could not be definitely ascertained whether in cardiac depression from chloroform, tonus was also roduced. Bruns,[12] however, was able to show definitely that tonus in the frog's ventricle is reduced when for long periods of time the heart is made to beat a very rapid rate, or compelled to work against increased resistance.

Compensation and Decompensation.—It is the dynamic function of the heart so to adjust its mechanisms that it, at all times, pumps the venous blood received into the systemic system under sufficient pressure to insure a continued capillary flow. As long as the heart does this, the circulation is compensated; when it fails to do so, decompensation occurs. The power of compensation is a physiological attribute of normal muscle tissues and is not necessarily linked with subsequent cardiac hypertrophy. This phase of the compensatory phenomenon may be well illustrated by reference to the acute production of a severe experimental lesion in animals. If, for example, the aortic valves are suddenly rendered incompetent, it will be found that the aortic diastolic-

pressure not only falls at once, but that the systolic pressure remains normal or rises above normal with the very next beat. The mechanisms through which this is accomplished operate somewhat as follows: With the first diastole, a small volume of blood regurgitates back into the ventricles. This not only distends the ventricles but elevates the initial tension. Consequently, during the next and every subsequent beat, not only the tension-maximum, but also the volumes ejected during systole are greater. Compensation for valvular defects then resolves itself into an increase in diastolic volume and initial tension which causes the heart to react, at once, by larger pressure curves and larger output.

Under what conditions does such immediate compensation fail to take place? Two suggest themselves: (1) If the tonus of the heart muscle, as defined, is low, augmented volumes may be accommodated within the ventricle without a proper elevation of initial tension. When this happens, the pressure-maximum reached within the ventricles and aorta are both lower and the discharge is actually decreased. (2) If the reserve power of the normal ventricle is exceeded, or if, through depressing agents, the normal reserve power is reduced, then also, decompensation supervenes. This necessitates an interpretation in more precise physiologic terms of the phrase "reserve power."

We have seen that every increase in diastolic volume and initial tension causes not only a larger systolic discharge but a higher pressure-maximum within the ventricles as well (Fig. 7). To this, as it has been experimentally shown, there is, however, a limit, for, if the initial pressure increases more and more, there comes a time when the pressure-maximum begins to decrease. Then the systolic discharge also decreases. The initial pressure at which this turning point occurs may be taken as the index of the reserve power of the ventricles. Whenever, therefore, the increase in initial pressure occasioned by a valvular defect rises above this point, the efficiency of ventricular contraction diminishes and decompensation begins. This safety mechanism whereby the ventricle is capable of responding at any moment's notice to larger initial tension, undoubtedly explains why decompensation does not, as a rule, occur in valvular lesions for many years, and that patients remain quite unaware of valvular disturbances which may be very marked.

The initial pressure at which the heart no longer responds with more vigorous beats and normal systolic discharge varies, not only in different animals, but in the same heart, e. g., when its blood supply is altered or when the heart muscle has been submitted to toxic depression or long continued strain. We have in this a clear explanation as to just how the condition of the myocardium finally determines whether compensation or decompensation takes place. For years, experiments

on artificial circulation machines (Marey,[4] Moritz,[24] etc.) had demonstrated that, whenever left heart valvular lesions occur, there is always a physical tendency for blood to dam back toward the right side, thus increasing pulmonary and right ventricular pressures. On the basis of such physical experiments, clinicians have long explained the pulmonary congestion and venous stasis observed in cardiac cases on the so-called "back pressure theory." It was, therefore, surprising that practically all experimental investigations of the various heart lesions (MacCallum and McClure,[25] Straub,[7] etc.) show that "back pressure effects" occur very seldom in lesions acutely produced in normal hearts. How are these observations to be interpreted? The physics of the body circulation is not different from that of artificial circulation machines. Back pressure effects should be and, as a matter of fact, would be produced, were it not for the immediate compensatory reactions called into play. When, in animals or in patients, this compensatory mechanism (i. e., the ability to respond to increased initial tension and volume by equal discharge and higher pressure-maximum) is lost, decompensation sets in. Then, and then only, "back pressure effects" take place.

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24. Marey: La Circulation du Sang **16**:136, 710.
25. MacCallum and McClure: Johns Hopkins Hosp. Bull. **17**:260, 1906; **22**:197, 1911.

INTERPOLATED CONTRACTIONS OF THE HEART WITH ESPECIAL REFERENCE TO THEIR EFFECT ON THE RADIAL PULSE *

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INTRODUCTION

Attention should be directed to some of the characteristics of interpolated contractions of the heart, particularly as they affect the radial pulse, since at times this type of cardiac irregularity is confusing.

An interpolated beat is a premature contraction of the ventricles which is not followed by a compensatory pause and does not disturb the dominant rhythm of the heart. It is impossible for auricular beats to be interpolated, because auricular premature beats are bound to disturb the dominant rhythm. It is also impossible to have interpolated beats in a case of complete auriculoventricular heart block, because here the dominant rhythm is ventricular, and so it, too, would be disturbed. Dresbach and Munford [1] state that interpolation in a case of Stokes-Adams' disease was reported by Lichtheim in 1905, but such a phenomenon is very unlikely. Inasmuch as interpolated beats can be no other than ventricular and must be premature, the cumbersome expression "interpolated premature ventricular contractions" can be discarded. In this paper we shall restrict ourselves to the term "interpolated beats." This form of premature beat is the only true "extrasystole," the term as it has been applied to the usual premature beat being unsatisfactory, since the heart rate in such a case is unchanged Interpolated beats are relatively infrequent but not so rare as has been stated by some authors. The A-V conduction is usually delayed following the interpolated beat, causing a delay in the appearance of the next normal pulse wave (Figures 1, 2, 3 and 4).

The mistake most frequently made, in the instances where wrong interpretations of the arterial pulse occur, is in stating that two premature beats appear, one immediately following the other; the first beat, the interpolated one, being designated as the first premature beat, while the next, which is the normal, is called the second premature beat. Again, a confusing picture may be presented where the regular occurrence of interpolated contractions every third beat, failing to reach the

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* From the Cardiographic Laboratory of the Massachusetts General Hospital.

1. Dresbach, M., and Munford, S. A.: Interpolated Extrasystoles in an Apparently Normal Human Heart, Illustrated by Electrocardiograms and Polygrams, Heart 5:197, 1913.

wrist, gives rise to pseudo-alternation. Three other very rare sources of error will be discussed later. This communication is presented in an effort to show wherein errors have been made and to simplify the diagnosis of this form of arrhythmia.

HISTORICAL

A résumé of the literature on this subject, up to 1914, appears in an article by Dresbach and Munford.[1] Busquet [2] stated that the first published tracing of interpolated beats was in the work of Marey,[3] in 1881. However, on examination no definite example was found by us among the 375 tracings in this book. It is possible that in Figure 355, page 723, such an irregularity appears, but it is more likely a bigeminal pulse due to very late premature beats. In an earlier publication by Marcy [4] a questionable interpolated beat appears in Figure 89, page 292. Uncertainty in diagnosis here is due to the fact that hiccup occurred at this moment, so that the picture is more likely the result of artefact. His Figure 202, page 524, may possibly contain interpolated beats.

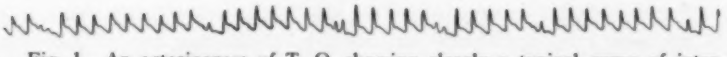

Fig. 1.—An arteriogram of T. O. showing clearly a typical curve of interpolated beats. Most of them can be easily seen; their amplitude varies and they are followed by normal beats of small size and delayed appearance. There is not always close relationship between the size of the interpolated beats and the size of the succeeding normal beats.

Wenckebach,[5] while correcting Mackenzie's error of interpreting an interpolated beat and its succeeding normal beat as two premature beats (Fig. 83, p. 99 of Mackenzie's "Study of the Pulse, Arterial, Venous, and Hepatic, and of the Movements of the Heart [6]") fell into the same error in his interpretation of his own Figure 10. Here the great delay in the appearance of the normal beat undoubtedly misled him. He republished in his book on the arrhyth-

2. Busquet, H.: Les Extra-systoles sans Repos Compensateur, Arch. d. Mal du Coeur, Paris **5**:187, 1912.

3. Marey, E. J.: Irregularités Périodiques du Pouls chez le Vieillard, Circulation du Sang. 1881.

4. Marey, E. J.: Physiologie médicale de la Circulation du Sang, Paris, 1863, Adrien Delahaye, Libraire-Editeur.

5. Wenckebach, K. F.: Zur Analyse des Unregelmässigen Pulses, Ztschr. f. klin. Med. **36**:181, 1898.

6. Mackenzie, J.: The Study of the Pulse, Arterial, Venous, and Hepatic, and of the Movements of the Heart, 1902.

mias [7] this same tracing with the same interpretation. Figure 9 of his book is correctly interpreted. Mackenzie's [6] Figures 53 and 54 probably contain examples of this condition. Trendelenberg [8] published tracings demonstrating interpolated beats as they were produced experimentally in frogs' hearts. One year later, in Hoffman's [9] writings, a good example appears in a poor tracing (his Fig. 5). Here the picture of pseudo-alternation is produced by the occurrence of interpolated beats, every third beat failing to reach the wrist. The true condition was unrecognized by the author. Also in 1904 Volhard,[10] in a paper on "Ventricular Bigeminy without Compensatory Pause, Resulting

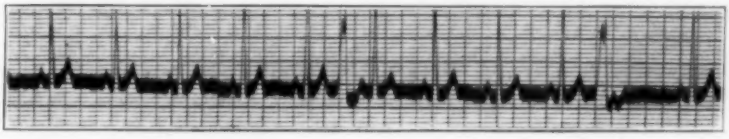

Fig. 2.—Electrocardiogram of T. O., Lead II. Here are shown premature beats of two types: the first interpolated; and the second a premature ventricular contraction with compensatory pause. The stimuli which provoke each contraction arise from the same point of the right ventricle in each instance. The *P-R* interval after the premature beat is greater than the *P-R* interval which precedes it.

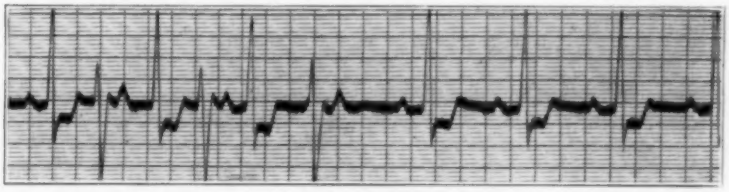

Fig. 3.—Electrocardiogram of Y (Lead II), a case of prolonged A-V conduction. The second and fourth contractions of the series are interpolated. The A-V conduction time is lengthened after the first, but practically no lengthening occurs after the second. The sixth beat is a premature contraction of the ventricle with full pause following. The remaining part of the curve is of normal rhythm, the prolonged conduction time being evident. All the premature beats arise from the same focus of left ventricle whether they are interpolated or not. The T wave shows evidence of digitalization.

7. Wenckebach, K. F.: Die Arhythmie als Ausdruck Bestimmter Functionsstörungen, Leipzig, Verlag von Wilhelm Englemann, 1903.

8. Trendelenberg, W.: Ueber ein Wegfall der Compensatorische Ruhe am Spontan Schlagenden Froschherzen, Arch. f. Anat. u. Physiol., Physiol. Abt., 1903.

9. Hoffman, A.: Ueber Verdoppelung der Herzfrequenz nebst Bemerkungen zur Analyse des Unregelmässigen Pulses, Ztschr. f. klin. Med. **53**: 1904.

10. Volhard, F.: Ueber Ventriculare Bigeminie ohne Compensatorische Pause Durch Rücklaüfigen Herzkontraktionen, Ztschr. f. klin. Med. **53**:475, 1904.

from Retrograde Ventriculo-Auricular Contraction," in his Figure 8 interprets the tracing as an interpolated contraction. By accurate measurements of the radial curve in this figure it is obvious that a pairing of premature beats occurs, no interpolation taking place. Pan [11] shows two striking demonstrations of the irregularity. In his Figure 15, a tracing from the cubital artery, interpolation occurs, the beat failing to appear in the sphygmographic curve. The succeeding normal beat is delayed and decreased in amplitude. There is also shown very clearly in Figure 23 the failure of an interpolated beat to reach the wrist, with marked delay and decrease in size of the next normal wave. Hay's little volume [12] contains three curves with all the interpolated beats coming through, the next normal beats being only slightly smaller

Fig. 4.—A radial curve of A illustrating what at first glance might be called a short paroxysm of tachycardia. On closer inspection it proves not to be. The first beat of the run of four is normal, the second interpolated, the third normal (slightly retarded) and the fourth a ventricular premature contraction with compensatory pause.

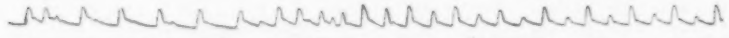

Fig. 5.—Radial tracing of E. D. showing an arrhythmia due to numerous interpolated contractions, in the last half of the tracing occurring every third beat and giving rise to a well-marked pseudo-alternation. There is delay in the small beats with non-appearance of the interpolated beats. In the middle of the tracing two of the interpolated contractions are clearly seen. At the beginning of the tracing there is an ordinary bigeminal pulse due to ventricular premature contractions every second beat, followed by compensatory pauses.

than the preceding normal pulse waves. Prolongation of the As-Vs interval following the interpolated beat is discussed by this author. Laslett,[13] in discussing a case showing the "Regular Occurrence of

11. Pan, O.: Ueber das Verhalten des Venen Pulses bei den durch Extrasystolen verursachten Unregelmässigkeiten des menschlichen Herzens, Ztschr. f. Exp. Path. u. Therap. **1**:57, 1905.

12. Hay, J.: Graphic Methods in Heart Disease, 1907.

13. Laslett, E. E.: The Regular Occurrence of Interpolated Extrasystoles, Heart **1**:83, 1909-10.

Fig. 6.—An electrocardiogram, Leads I and III, of E. D. Three interpolated contractions appear in Lead I and following each the *P-R* interval is slightly lengthened. Three interpolations are seen also in Lead III. This electrocardiogram confirms the interpretation of the radial tracing of Figure 5. Abscissa = 0.2 sec., ordinate = 10-4 volt. These same measurements apply to the electrocardiograms following.

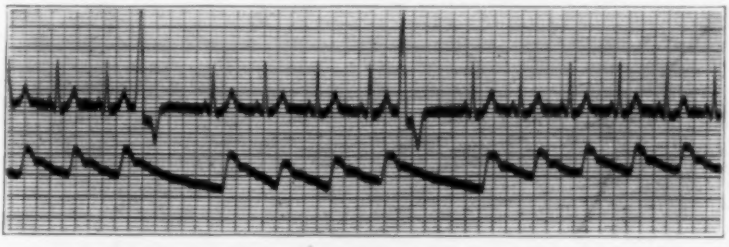

Fig. 7.—Simultaneous electrocardiogram (Lead II) and sphygmogram from radial artery (E. D.). This and the three following figures are from the same patient, all taken on the same occasion. Here is seen the appearance of premature ventricular contractions at two points; in neither instance does the beat show in the radial curve.

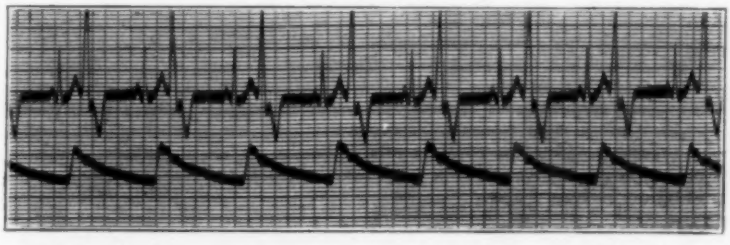

Fig. 8.—Simultaneous electrocardiogram (Lead II) and arteriogram (radial) (E. D.) which shows a perfectly regular radial pulse with a rate between 40 and 50 per min., the result of the regular occurrence of premature ventricular contractions every second beat, failing to reach the wrist.

Interpolated Extra-Systoles," states that the marked prolongation of the As-Vs interval following the interpolated beat does not seem to be the rule, the exact significance of this factor with regard to the origin of the compensatory pause not being clear. An excellent illustration of pseudo-alternation due to interpolated beats every third beat, not reaching the radial curve, is given by Gallavardin and Gravier.[14] The small normal contractions are considerably delayed. An incorrect interpretation by Mackenzie in his "Diseases of the Heart" [15] (p. 208, Fig. 118), is indicated by analysis of the jugular pulse tracing. Undoubtedly, the delay in the appearance of the normal beat, marked by Mackenzie as

Fig. 9.—Simultaneous electrocardiogram (Lead II) and radial curve (E. D.). A short phase of normal rhythm is interrupted by an interpolated contraction, which irregularity persists throughout the remainder of the tracing. The occurrence of the interpolated beats every third beat and their failure to come through to the radial artery gives a characteristic picture in the sphygmogram.

Fig. 10.—Simultaneous electrocardiogram (Lead II) and radial tracing (E. D.). Interpolated contractions occur regularly every third beat producing very prettily a picture of constant alternation in the sphygmogram. With the electrocardiographic curve as a guide in this case, the interpretation of the arteriogram is very simple.

14. Gallavardin, L., and Gravier, L.: Quelques Particularités de l'Alternance du Pouls: Variété du Pouls Pseudoalternant; Couples Extra-systoliques et Alternances; Changements de Sens Spontanés de l'Alternance, Arch. d. mal. du Coeur **7**:497, 1914.

15. Mackenzie, J.: Diseases of the Heart, Ed. 3, 1913.

the second *r'*, misled him. The high wave in the jugular pulse during the long radial intermission is made up of *a* and *c* and not *a* alone or *a* and *v*. There occurred here an alternation of the normal and premature beats, the first premature beat interpolated and the second following by a compensatory pause but failing to reach the wrist. In "Clinical Cardiology" [16] Neuhof published a radial tracing (Fig. 153, p. 71) the small beat of which he refers to as "an extrasystole which is not premature"; the disorder is almost certainly due, however, to the interpolation of a contraction which failed to reach the wrist, but which reduced in size and delayed the next normal beat. Lewis [17] gives a few curves showing interpolation. Figure 165, page 208, in his new edition, is an electrocardiogram in which there are two interpolated contractions, with very slight As-Vs lengthening following them. Also, Figure 164, page 208, a simultaneous record of electrocardiogram, phlebogram and sphygmogram, contains a single interpolated beat. This fails to change the sphygmogram, except to delay the next normal wave about one-tenth second. Length-

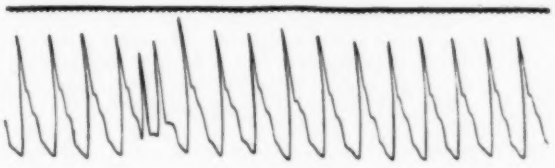

Fig. 11.—A sphygmogram of S. showing four beats of the normal rhythm followed by an interpolated contraction. The succeeding beat, the normal, is slightly delayed and decreased in amplitude. Time intervals 0.2 sec. In all further arteriograms the same time interval is recorded.

ening of the P-R interval occurs. Lewis states that the reason for the prolongation is obscure since the extra beat has not been propagated through the A-V bundle. However, it may have traversed the A-V bundle and been stopped at the auriculo-nodal junction which is the point of greatest retardation in the A-V conduction. Lewis' statement that the larger the pulse wave of the interpolated beat, the smaller is the succeeding pulse, is not always borne out (see our own Figure 1). Figure 98, page 150, of Lewis' new edition,[17] an experimental curve from the dog's carotid simulates very closely the picture produced in man by an interpolated beat failing to reach the wrist followed by a weak normal wave. A simultaneous curve taken directly from the ventricle proves that the weak beats are much delayed premature ven-

16. Neuhof, S.: Clinical Cardiology, 1917.
17. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, 1920.

tricular contractions, and not due to normal beats delayed as the result of interpolated contractions which failed to reach the carotid. This possibility must be kept in mind in the arterial tracings from man, although, as Lewis states, "it is but rarely responsible for an inaccurate interpretation."

OCCURRENCE

Among 5,000 electrocardiographic plates taken of 2,392 subjects in the Cardiographic Laboratory of the Massachusetts General Hospital from 1914 to 1920, ventricular premature beats occurred in 284 plates of 200 patients, not including the ectopic beats of auricular fibrillation or of complete heart block. They were interpolated in twenty-four of these plates (8 per cent.), and in fourteen patients (0.6 per cent. of total patients, and 7 per cent. of cases showing premature beats). After for-

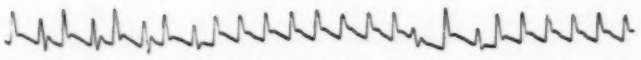

Fig. 12.—Radial curve beginning as bigeminy due to interpolated contractions every third beat, failing to reach the wrist. Then follows a phase of normal rhythm, a premature ventricular contraction with compensatory pause, and an interpolated beat, which does not come through.

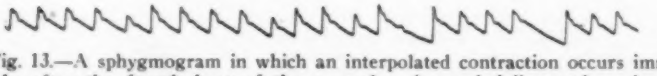

Fig. 13.—A sphygmogram in which an interpolated contraction occurs immediately after the fourth beat of the normal series and fails to show in the curve. A delayed small normal beat follows; then a run of four normal waves and the process is repeated. Two more normal beats come through and we see the same anomaly again. The last two interruptions are the result of premature contractions of the ventricle with compensatory pauses.

ty-two interpolated beats of these fourteen patients, there was definite prolongation of the P-R interval; in three instances there was no prolongation; and in thirty-four the prolongation was questionable. In one case it was observed that in the presence of sinus arrhythmia associated with interpolated beats, during the rapid rates of the auricular pacemaker, the P-R interval was much delayed, but that it was normal or only slightly delayed during the slower intervals.

The significance of the interpolated beat is just that of the premature ventricular beat generally—that is, the interpolated beat is evidence of an irritated heart, but not necessarily of heart disease. Its

presence adds nothing to the prognosis of a given case. Of our fourteen patients, six showed evidence of heart disease; four were questionable, and the other four showed merely an irritated heart. One of the last four, (Figs. 5, 6, 7, 8, 9 and 10) has had an intermittent pulse for fifteen years, but has had no other cardiac symptoms than the occasional palpitation. The interpolated beat is merely a rare variety of premature ventricular contraction. Nearly every case showing it also shows at other times the usual ventricular premature beat with compensatory pause. The slower the pulse the more apt is the ventricular premature contraction to be interpolated, for in such an instance the ventricle will have recovered from its refractory phase following its interpolated contraction when the next normal auricular impulse reaches it.

DIFFERENTIAL DIAGNOSIS

The interpolated beat in the arteriogram must be differentiated especially from two other conditions with which it is apt to be confused. These are: (1) the occurrence of successive ventricular premature contractions; and (2) pulsus alternans. In the historical résumé we have already mentioned this possibility of confusion. Without venous pulse tracings or electrocardiograms the diagnosis may at times be difficult.

Often the analysis of the radial tracings where interpolation occurs is simple, the interpolated beat fitting in between two normal beats with very little delay in the time or decrease in the amplitude of the second normal beat (Fig. 11). The occurrence of two successive ventricular beats is uncommon. In the Cardiographic Laboratory of the Massachusetts General Hospital, among 260 electrocardiograms of 186 patients showing premature ventricular contractions (not including those showing interpolated beats together with premature ventricular contractions with pauses) pairing of these premature beats was found in twenty-one plates. There was a total of ninety-eight instances of pairing, seventy-four of these having occurred in nine plates of one patient. Therefore, leaving out of consideration this one case in which they occurred so frequently, we have the appearance of consecutive premature contractions twenty-four times in only twelve out of the 251 different plates of 185 patients. Among these ninety-eight instances where pairing occurred, accurate measurement was possible in only sixty-five, and in only six of these did the interval during the pairing equal the space between two normal beats. In three instances the interval was equal to the space between three normal beats, which condition cannot occur in the case of interpolated beats. In the other fifty-six instances the space over the pair was unequal to either two or three normal beats but fell between these two measurements or between

the measurements of three and four normal beats.[18] When in doubt, an electrocardiogram is necessary to distinguish between the interpolated beat disorder and the occurrence of a pair of ventricular premature beats.

The second condition which may be confused with interpolated contractions is constant alternation of the pulse, in which the weak beats are considerably delayed (Figs. 5, 10 and 12). This difficulty occurs rarely, because it necessitates the absence in the radial pulse of all evidence of the interpolated beats themselves. In such a case an electrocardiogram or jugular pulse tracing clears up the situation at once. We have found constant alternation much more common than constant pseudo-alternation due to interpolated beats. In only two cases have we discovered this type of pseudo-alternation, a possibility rarely recognized.

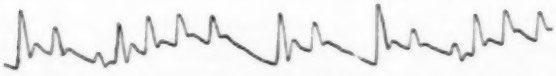

Fig. 14.—Tracing from radial artery. Near each end of the curve two very small waves are seen. These are the normal contractions which have been preceded by interpolated beats failing to show in the tracing. Near the center the two long intermissions are produced by ventricular premature contractions, failing to reach the artery, and followed by full pauses.

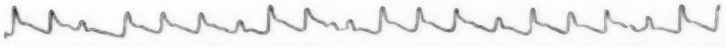

Fig. 15.—A sphygmogram of T. O. illustrating a premature ventricular beat of the usual type, it being at the first point of interruption of the regular rhythm in the tracing. Then follow three normal beats. In the remainder of the curve four interpolated beats varying in amplitude occur, and in each instance a small delayed normal contraction follows.

A third possible source of error in the analysis of radial tracings in arrhythmia due to interpolation is the infrequent return to one-to-one rhythm for three beats in long stretches of two-to-one auriculoventricular heart block. In both instances the time of the two short intervals is greater than that of one long space because of the increase in the P-R interval. In such rare instances electrocardiograms or jugular pulse tracings are necessary for differentiation. We have seen one

18. This break in the dominant rhythm is due to retrograde contraction of the auricle following one or the other or both of the ventricular premature beats.

such case of heart block which might be confused with the interpolated contraction, but the radial pulse was not of characteristic form.

A fourth arrhythmia to be differentiated from the interpolated beat in the arteriogram is the premature ventricular contraction occurring at every fourth beat and failing to reach the wrist. Here, also, venous pulse tracings or electrocardiograms quickly differentiate, but the arteriogram itself is usually quite different in form from that of the interpolated beat arrhythmia in that the beats of the normal rhythm are evenly spaced and uniform in amplitude, which is not the case in interpolation.

A fifth condition to be considered in the differential diagnosis are short runs of paroxysmal tachycardia. Occasionally, one finds interpolated beats occurring every other beat, as in Dresbach and Munford's [1] case, and for a few beats in our Figure 3. In this figure two such interpolated beats are shown, and the third beat is followed by a compensatory pause. The pulse, upon palpation or auscultation of the heart, would have shown in this case six beats in rapid succession and might have simulated a short paroxysm of tachycardia. In

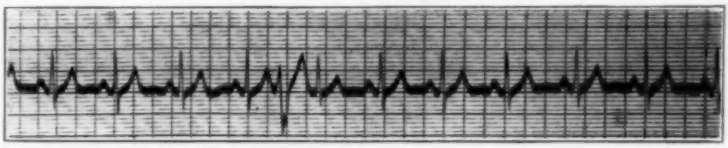

Fig. 16.—An electrocardiogram of S. T. in which one interpolated contraction occurs after the fourth beat of the normal rhythm. The large wave succeeding results from the falling together of the *T* and *P* waves. Note the lengthening of the *P-R* interval after this contraction.

Figure 4 there is shown a short phase of four beats in rapid succession. Here the interpretation undoubtedly is as follows: the first of the four is normal, the second is an interpolated contraction, the third is normal, and the fourth a premature ventricular contraction followed by a compensatory pause.

Figures 13 and 14 illustrate two radial pulses difficult at first glance to interpret. In Figure 13 two long pauses appear in the tracing, one with a poorly marked premature beat in evidence, while in the other a premature beat takes place but is not forcible enough to come through and appear in the curve. At the beginning and middle of the tracing are three delayed and diminished beats which follow interpolated contractions too weak to reach the radial artery. It is this abnormality in the arteriogram which has puzzled a good many students but which is perfectly typical and easily recognized as soon as one is familiar with it. Figure 14 shows likewise two small beats which are the normal

contractions following interpolated beats, not reaching the wrist. Two long intermissions are also seen due to premature ventricular beats with compensatory pauses. These also do not appear.

Figures 7, 8, 9, and 10 are tracings from a single patient who has shown various forms of arrhythmia of the pulse as a result of premature ventricular and interpolated beats. In Figure 7 are shown simple premature beats with pauses, the beats not coming through to the wrist. Figure 8 shows the regular occurrence of premature contractions every second beat, none of them being forcible enough to produce a wave. It illustrates a slow, dead regular pulse the palpation of which, alone, at this particular time would not suggest the presence of premature beats. In Figure 9 we note the onset of a phase of arrhythmia due to interpolated beats, every third beat not coming through. And Figure 10 shows a continuation of this same rhythm. These last two illustrations show in a very clear manner the mechanism of the usual effect on the radial pulse of interpolated beats and illustrate one type of pseudo-alternation. If the reader will familiarize himself with the arrhythmia found in these figures he will save a good deal of effort in the future in analyzing such curves.

SUMMARY

There is here given a brief historical review of the subject of interpolated beats. Figures are given stating the frequency with which interpolated beats and premature ventricular contractions have been found in the graphic records of the Cardiographic Laboratory of the Massachusetts General Hospital. Points in regard to the differential diagnosis of this form of arrhythmia are discussed; the five conditions from which it must be differentiated in the arterial pulse being: first, the occurence of two premature ventricular beats in succession; second, constant alternation of the pulse in which there is a delay in the weaker beats; third, auriculoventricular heart block associated with an occasional return to one-to-one rhythm for three beats in long stretches of two-to-one rhythm; fourth, arrhythmia due to the premature beats every fourth beat which fail to appear in the arteriogram; and fifth, short paroxysms of tachycardia. Emphasis is laid upon that type of tracing which is most frequently misinterpreted, namely, where in the course of a phase of regular rhythm there occurs an interpolated beat which, not showing in the curve, causes a delay and diminution in the size of the next normal wave. Insufficient emphasis has been put in the past on this abnormality in the arteriogram, and it is on this that we lay special stress.

BOOK REVIEW

PRINCIPLES OF HUMAN PHYSIOLOGY. By Ernest H. Starling, C.M.G., F.R.S., etc., Jodrell Professor of Physiology in University College, London. The chapter on the sense organs revised and largely rewritten by H. Hartridge, M.A., M.B., Cantab. Ed. 3, with 579 illustrations, 10 in color. Philadelphia, Lea & Febiger, 1920.

The success of Starling's Physiology, as shown by reaching a third edition in eight years, is to be explained by the author's high standing as experimenter and teacher, by the clearness of the statement and well chosen arrangement of the work, and these warrant its use by beginners. There is one curious feature, over 100 pages, or almost one-eleventh of the total space, is devoted to vision. Perhaps, the vagaries of the medical book trade are to blame for this; perhaps, lack of time to condense the material into space proportionate to that of other topics. In strong contrast to this large chapter, the ear and its associated organs are discussed in a few pages. Perhaps, Bárány's work was made too prominent by certain specialists during the war, but that seems all the greater reason why a clear and authoritative summary should be given.

Readers of the Archives of Internal Medicine are not much interested in a work on physiology prepared for beginners. When a large volume appears, they turn to it for definite reasons. They may wish to review again the whole subject. If so, they will find much of interest in the chapters on the Structural Basis of the Body and on the Material Basis. They will be interested in seeing that the word "proteid," preferred by some writers, is avoided by the author on account of its misleading use. They will find much clarifying discussion on colloids, ferments, electric changes in muscles and nerves. Those who seek information on topics much written about in current journals, but little known in undergraduate days, will often be disappointed. The chapter on metabolism is clear, concise and accurate as far as it goes, but of little assistance to the physician who wishes to get his knowledge abreast of the times by taking a laboratory course. One who is puzzled by statements about respiratory quotients, for example, will have trouble coordinating the information scattered over several different sections. Everywhere the lack of reference will disappoint the mature reader, or in fact, anyone qualified to read a textbook of 1300 pages. The brief remarks on vitamins is characteristic of many parts that read like abstracts noted for further elaboration. The practitioner or the young researcher who seeks an up to date presentation of the subject of digestion will find a praiseworthy impartiality as to the identity of rennin and pepsin. He will find mention of Pawlow, even a reference to the English translations of the work on the digestive glands, also to Cannon, but of other, more recent writers, not a word. Clinical references are conspicuous by their absence. It is all the more striking to find under "gout" the statement that "in normal individuals the amount of uric acid in the blood is too small to be detected." The reader seeking recent light on the D: N ratio will look in vain in the index, but will find the subject well stated in the chapter on the history of fat in the body. Alkaline reserve and hydrogen ion concentration are adequately presented. Can the young clinical pathologist get any satisfaction from the statement that blood platelets are "precipitates produced in the plasma directly it undergoes alterations"? Should not the fact that there is an auscultatory method in blood pressure determination be, at least, indicated? The older practitioner, puzzled by the flood of electrocardiographic papers, and turning to Starling for the explanation of auricular fibrillation, will find nothing in the index and little in the text. That little is good, though dogmatic and undocumented. Extrasystole does not fare so well. If the author knows the record of pulse rates of 30 and 120 in men otherwise

perfectly healthy, references would seem worth while. Very satisfactory are the chapters of cellular and chemical methods of defense, also that on the chemistry of the respiration, as was to be expected. The author is rarely finicky, but what else can one call it when he criticizes the common use of "expiratory dyspnea." Perhaps, it is a slip of the pen that translates 37 C. as 98.4 F. instead of 98.6 F. The chapters on urine are good, Cushny's work being mentioned often. That on the ductless glands is too short. On the whole, Starling is not likely to be used much after undergraduate days. Perhaps, the belief that it will not be used explains the poor paper and the flimsy binding, or is the latter an indication of sabotage? The reviewer's copy has the text fastened to the back only by what looks like mosquito netting.

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